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Behavioral economics and drug choice: effects of unit price on cocaine self-administration by monkeys

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The application of microeconomic theory to the experimental analysis of behavior has been termed behavioral economics. There has been an increasing interest in applying the concepts of behavioral economics to the study of drug self-administration. In a previously published experiment (Nader and Woolverton, 1992), rhesus monkeys (N = 3) were trained in a discrete-trials choice procedure and allowed to choose between intravenous injections of cocaine (0.03 - 1.0 mg/kg/injection) and food presentation (1 or 4 pellets; 1 g/pellet) during daily 7-h experimental sessions. When cocaine or food was available under a fixed-ratio (FR) 30 schedule, cocaine intake increased in a dose-related manner for all monkeys. When the response requirement (FR) for cocaine was differentially increased by doubling or quadrupling, the frequency of cocaine choice decreased, shifting the cocaine dose-response function to the right. The present paper is a reanalysis of data from that experiment. Several mathematical models, differentially incorporating the effects of FR, dose and number of food pellets, were compared. When cocaine consumption was analyzed using a multiple linear regression analysis with FR, dose and number of pellets as separate main effects (model I), the R^2 was 0.82. When FR and dose were combined into one factor, unit price (UP, responses/mg/kg), and cocaine consumption was analyzed as a linear function of UP (model IIA), the R^2 was 0.54. When cocaine consumption was analyzed as a curvilinear, negatively accelerated function of UP (model IIB), the R^2 was 0.53. The difference between models I and IIA was statistically significant while models IIA and IIB were not different. Since the choice was mutually exclusive, cocaine consumption was analyzed as a function of the ratio of the UP of cocaine and the UP of food, the reinforcer that was lost when drug was chosen. The R^2 for this analysis was 0.58. Multiplying that ratio by the sum of the UPs for cocaine and food (Bickel, personal communication) resulted in an increased R^2 of 0.64. Eliminating data from low dose conditions (Bickel, personal communication) improved the fit of model IIB but not of I or IIA. Thus, a UP analysis of cocaine consumption under the present conditions significantly decreased the proportion of the variance that was accounted for by the multiple linear regression model. These results suggest that changes in FR and dose do not necessarily have the same functional effect on drug consumption and that the applicability of the UP model to drug self-administration may be limited.

Key words: discrete-trials choice; self-administration; cocaine; behavioral economics; alternative reinforcer; rhesus monkey

The application of the concepts of microeconomics to the experimental analysis of behavior has been termed behavioral economics (Green and Kagel, 1987). Recently, it has been suggested that drug self-administration can be analyzed in this framework (Bickel et al., 1990, 1991; Hursh, 1991; Degrandpre et al., 1992). For example, Bickel et al. (1990) reanalyzed data from several experiments and showed that drug consumption by animals under a variety of conditions was a decreasing function of unit price (UP, responses/mg/kg) and that the shape

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of the function relating consumption to UP (demand curve) was similar under a variety of experimental protocols. One implication of this observation was that changes in response requirement and dose have the same functional effect on drug consumption. The generality of these conclusions remains to be established. UP analysis of drug consumption by animals when alternative reinforcers are simultaneously available has received little attention (Carroll et al., 1991).

For the past several years we have been using a discrete-trials choice procedure to study environmental and pharmacological determinants of the reinforcing effects of i.v. cocaine in rhesus monkeys (e.g., Woolverton and Balster, 1981; Woolverton and Johanson, 1984; Nader and Woolverton, 1991, 1992). In one experiment (Nader and Woolverton, 1992), rhesus monkeys were trained to choose between an injection of cocaine and the delivery of food pellets. Under baseline conditions, either reinforcer was available under a fixed-ratio (FR) 30 schedule, and the frequency of cocaine choice increased directly with dose. Differentially increasing the response requirement (FR) for cocaine by doubling or quadrupling decreased the frequency of cocaine choice and shifted the cocaine dose-response function to the right.

The purpose of the present paper was to examine the effect of UP on cocaine consumption by monkeys in the Nader and Woolverton (1992) experiment using several models involving UP and to directly compare the fit of those models with a more traditional dose-response function analysis. To do this, data from that experiment were reanalyzed and compared using several statistical models that differentially incorporated the effects of FR, dose and number of food pellets. In the first model, the influence of dose, FR and number of pellets was assessed using the following linear regression equation:

(I) $y = a + b(\ln FR) + c(\ln dose) + d(number\ of\ pellets)$

where y = ln (consumption) in mg/kg/session. The second model combined FR and dose into one independent variable, UP (ln[FR/dose]), and consumption was described as shown in IIA:

(IIA) $y = a + b(\ln [cocaine\ UP]) + c\ (number\ of\ pellets)$

Hursh (1991) has proposed that a non-linear relationship which includes UP in its raw metric, in addition to the log-transformed UP, provides a better description of consumption. This equation, shown in IIB, was also evaluated in the present manuscript.

(IIB) $y = a + b(\ln[cocaine\ UP]) + c(cocaine\ UP) + d(number\ of\ pellets)$

The third model was based on the fact that in discrete-trials choice procedures the reinforcers are mutually exclusive. Thus, the choice situation may be thought of as having two UPs operating simultaneously: the UP for the obtained reinforcer (e.g., cocaine UP) and an additional price incurred by the loss of the opportunity to obtain the alternative reinforcer, at least until the next trial. That is, total price could be considered as a ratio of the two UPs: [cocaine UP]/[food UP]. Thus, the third model incorporated all three main effects into one factor, the ratio of UPs, and consumption was described using the non-linear equation shown in III:

(III) $y = a + b(\ln([cocaine\ UP]/[food\ UP])) + c([cocaine\ UP]/[food\ UP])$

The UP for food was 30/1 pellet or 30/4 pellets.

Behavioral economics predicts that consumption should be the same at a given UP, irrespective of the combination of response requirement and dose that make up that UP. However, Bickel (personal communication) has found that this outcome is not always realized and has proposed a modification of the calculation of UP ratio (see Bickel et al., 1993) that involves multiplying the ratio by the sum of the UPs for the two reinforcers. The utility of this multiplier (cocaine UP + food UP) was evaluated in the present manuscript using the equation shown in

III. Finally, it has been suggested by Bickel (personal communication) that data collected at low doses may not fit the UP model, perhaps because they are too low to function as reinforcers. Therefore, the present data were also analyzed with outliers from the low dose condition removed.

Methods

The behavioral methods have been described in detail previously (Nader and Woolverton, 1992). Briefly, three adult male rhesus monkeys (*Macaca mulatta*) which weighed between 6.0 – 10 kg under free-feeding conditions, served as subjects. Their body weights were decreased to approximately 90% of free-feeding weights, and maintained at that level for the duration of the experiment, by food delivered during experimental sessions (1 g banana-flavored pellets, P.J. Noyes, Co., Lancaster, NH) and supplemental feeding of Purina Monkey Chow no sooner than 30 min post-session. In addition, monkeys were given a chewable multiple vitamin tablet 3 days/week and occasionally received fresh fruit. Monkey 88-15 was experimentally naive, while the other monkeys had been used in a previous experiment investigating food-drug choice behavior (see Nader and Woolverton, 1991).

Each monkey was fitted with a stainless-steel restraint harness and spring arm that attached to the rear of an experimental cubicle equipped with 2 response levers, a food pellet dispenser and a peristaltic infusion pump for delivering drug injections. The four stimulus lights above the left lever (lever 1) were covered with white lens caps, while two lights above the right lever (lever 2) were covered with red and two with green lens caps. In addition, two houselights, one white and one red, were mounted on the ceiling of the cubicle and were covered with translucent plexiglas.

Each monkey was anesthetized with a combination of ketamine and halothane and a chronic indwelling silicone catheter was inserted into a major vein. After a 1 – 2 day recovery period, each was allowed to choose between various doses of cocaine and food under a discrete-trials choice procedure (see Nader and Woolverton, 1992 for details). The beginning of a choice trial was signalled by the illumination of the overhead white houselight, all four lever 1 lights and either the red or green lights above lever 2. Responding on lever 1 changed the lights above lever 2 from red to green or vice versa. The first response on lever 2 after at least three stimulus changes extinguished the houselight and the lights above lever 1. Completion of a FR 30 on lever 2 within 5 min (limited hold, LH 5-min) resulted in either an injection of cocaine (1.0 ml/10 s) or the delivery of four food pellets. A 10-min time-out (TO) followed completion of a trial or expiration of the LH. After the TO, a new trial began. Sessions ended when (a) 30 trials were completed or (b) 7 h elapsed or (c) a monkey had received its daily allotment of food (100 – 120 g/day, individually determined), whichever came first.

Three variables were systematically manipulated: cocaine dose (0.03 – 1.0 mg/kg/injection), FR for cocaine (FR 30, 120, 240, 480 or 960) and magnitude of food reinforcement (1 or 4 pellets). When FR 480 or 960 were studied, the LH was increased to 10 min. Each condition was in effect for at least 5 consecutive sessions and until choice behavior was stable (± 15% of the mean with no consistent trends) for at least three consecutive sessions. The minimum number of sessions for a condition was individually determined and based upon the number of sessions that were required for preference to return when the stimuli paired with each reinforcer were reversed.

Data analysis

The data previously published and analyzed were presented as a relative measure, % of total trials in which cocaine was chosen. Because the primary dependent variable in behavioral economic theory is consumption, the present manuscript presents the data as total cocaine intake (mg/kg/session). Means were calculated for individual monkeys over the last three sessions of a condition and data were analyzed using

group means ($N = 2-3$). Separate multiple regression analyses (SPSS Software for Macintosh) were used to describe consumption in an effort to directly evaluate the utility of analyzing the data in behavioral economic terms. Included in each analysis were t-statistics computed for each independent variable in the model. In addition, an R^2 value which described the total amount of variability accounted for by the model was also computed. For the present analysis, a more conservative adjusted R^2 value, based on differences in degrees of freedom, was used for all analyses. The R^2 values associated with models I and IIA were directly compared by an F-test; models IIA and IIB were also compared using an F-test. In addition, because it is possible that consumption as a function of price may be more variable at low doses, all models were re-evaluated when data obtained from the lowest dose of cocaine (0.03 mg/kg/injection) were omitted.

Results

Comparison of the three models

Cocaine consumption increased directly with dose of cocaine ($t[17] = 9.67$; $P < 0.001$) when either one or four pellets was the alternative (Fig. 1). Differentially increasing the FR for cocaine decreased cocaine intake under both pellet conditions [$t[17] = -3.97$; $P < 0.001$]. The effect of increase in FR tended to be greater under the four-pellet than under the one-pellet condition, though this effect did not reach statistical significance [$t[17] = -2.00$;$P < 0.06$]. The R^2 value for the linear regression model fit to the data shown in Fig. 1 was 0.82. Beta values, which are standardized estimates (in standard deviational units) of the contribution of each independent variable in predicting consumption, indicated that the cocaine dose influenced cocaine consumption the most ($\beta = 1.06$), followed by FR value ($\beta = -0.44$) and magnitude of food reinforcement ($\beta = -0.19$).

Cocaine consumption generally decreased with increases in UP (Fig. 2; $t[18] = -4.99$; $P < 0.001$, model IIA). There was no significant difference in the effect of UP between the one- and four-pellet alternative. The R^2 value was for this model, 0.54 which was significantly lower than the R^2 generated from model I ($F[1, 17] = 29.86$; $P < 0.001$). Thus, combining FR and dose into one variable (UP) significantly

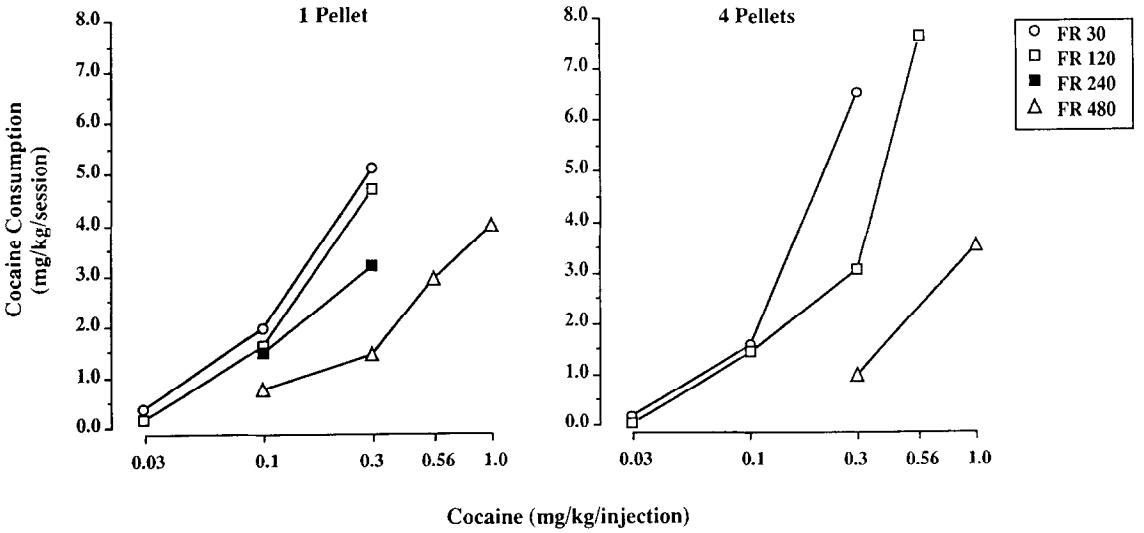

Fig. 1. Cocaine consumption (mg/kg/session) as a function of cocaine dose. The alternative reinforcer to cocaine was either one (left panel) or four (right panel) food pellets, available under a FR 30 schedule. Cocaine was available under different FR schedules, represented by different symbols. Each point is the mean of the last three sessions of a condition for two or three monkeys.

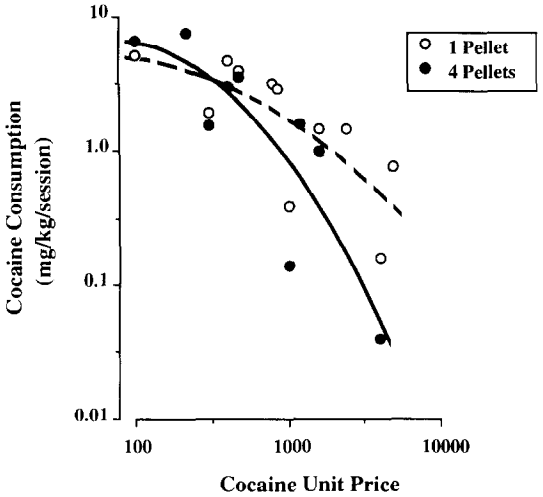

Fig. 2. Cocaine consumption (mg/kg/session) as a function of cocaine unit price. The alternative reinforcer to cocaine was either one (open symbols) or four (closed symbols) food pellets, available under a FR 30 schedule. A best-fit line of the data when one (dashed line) and four (solid line) pellets were the alternative is also shown. Each point represents the mean of 2 or 3 monkeys.

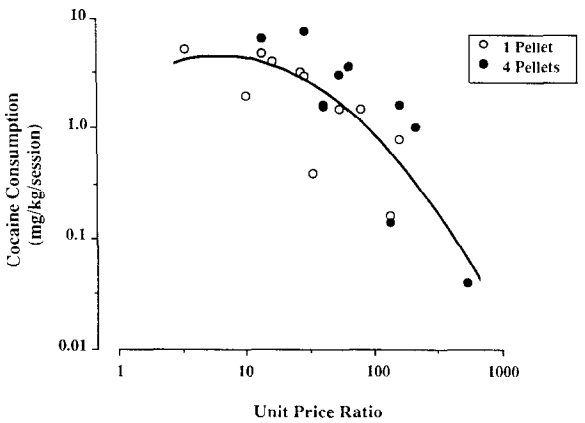

Fig. 3. Cocaine consumption (mg/kg/session) as a function of the ratio of cocaine unit price and food unit price . The unit price ratio when one pellet was the alternative is represented by open symbols, while the unit price ratios in which four pellets were the alternative are represented by closed symbols. A best-fit line of the data is also shown. Each point represents the mean of 2 or 3 monkeys.

decreased the amount of variability accounted for by the model. This indicates that the restriction caused by combining the two independent variables FR and dose into one independent variable (UP) significantly decreases the fit of the model to the data. There were several cases where consumption varied more than fivefold at similar UPs. The beta values were −0.77 and −0.24 for UP and magnitude of food reinforcement, respectively. The R^2 for the non-linear model (IIB), 0.53, was not significantly different from that of the linear model.

Cocaine consumption generally decreased with increases in UP ratio Fig. 3; $F[2,18] = 15.03$; $P < 0.001$). The R^2 for this model was 0.58, although the individual t-statistics showed that only the effect of UP itself was significant ($t[18] = -2.1$, $P < 0.05$). As with UPs, there were several cases where consumption varied more than five-fold at similar a UP ratio. When the data were reanalyzed with the UP ratio multiplied by the sum of the UPs, cocaine intake was significantly influenced by both the ln (UP ratio) ($t[18] = -2.73$; $P < 0.01$) and UP ($t[18] = -2.18$; $P < 0.05$). Beta values were −0.50 and −0.40, respectively. The R^2 was 0.64 with the multiplier included in the equation.

Elimination of outliers

Only the dose of 0.03 mg/kg cocaine maintained consumption of less than 0.5 mg/kg/session (Fig. 1). Those points deviated substantially from the functions shown in Figs. 2 and 3. Therefore, models I, IIB and III were re-examined with the data obtained from 0.03 mg/kg/injection cocaine removed from the dataset (Table I). For the analysis involving UP ratios, the multiplier was included since it proved to be a better predictor of consumption. The variability in consumption accounted for by the dose-response function model (I) and the UP

Table I. Effects of low-dose choice behavior on the R^2 value for each model

Model	0.03 - 1.0 mg/kg	0.1 - 1.0 mg/kg
I. Dose-response function	0.82	0.79
IIB. Unit price	0.53	0.62
III. Unit price ratio*	0.64	0.64

*This model includes the multiplier term (see text for details).

ratio model (III) were not substantially changed. In contrast, R^2 increased for model IIB. Nevertheless, comparison of the R^2 values still revealed a large difference in the proportion of the variance in cocaine consumption accounted for by models I and IIB ($F[1,13] = 10.53; P < 0.01$).

Discussion

As has been reported previously (Nader and Woolverton, 1991; 1992), cocaine consumption was an increasing function of dose and a decreasing function of FR in monkeys given a choice between cocaine and food. In addition, cocaine consumption was a decreasing function of UP, a finding that is consistent with previous reports of the effects of UP on drug consumption (Bickel et al., 1990, 1991; Carroll et al., 1991). However, a model that considered FR, dose and magnitude of the alternative reinforcer as separate effects accounted for a larger proportion of variance in total cocaine intake than did the UP model. This finding suggests that, at least under some conditions, a better understanding of the variables that control drug consumption can be achieved by treating each of the independent variables (FR and dose) separately rather than considering them as the ratio defined by UP. That is, the present analysis implies that changes in response requirement and dose do not necessarily have the same functional effect on drug consumption.

The fact that the R^2 for the UP model in the present experiment was lower than has been found by other investigators (Bickel et al., 1991) suggests that the generality of the UP model of drug consumption is limited. The basis of that limitation is unclear. Possibilities include aspects of the drug, the environment, or the organism. Intravenous cocaine self-administration may be somehow different from other drugs or routes of administration. However, the abundant data demonstrating the similarities between cocaine-maintained behavior and behavior maintained by other drug or non-drug reinforcers makes this unlikely (Johanson and Fischman, 1989). Although species may have been a determinant, Carroll et al. (1991) reported good UP prediction of consumption of phencyclidine by rhesus monkeys. Similarly, it seems unlikely that the choice situation itself was responsible since Carroll et al. (1991) studied choice between PCP and a non-drug reinforcer. It is possible that the mutually exclusive nature of the choice in the present experiment with the added consequence of loss of the alternative reinforcer may be important. Additionally, some other parameter of the present procedure (e.g., duration of the TO) may have affected the outcome. Moreover, the nature of the alternative reinforcer may contribute in some, as yet, unspecified way (e.g., substitute vs. non-substitute; cocaine-induced anorexia). One intriguing possibility has to do with the pharmacological determinants of drug consumption. Unrestricted drug consumption is determined not only by the reinforcing effects of the drug but also by the direct effects of the drug on responding. Thus, in the data reviewed by Bickel et al. (1990), the shape of the demand curves was undoubtedly influenced by a combination of drug effects. By contrast, in the present experiment we attempted to minimize the influence of the direct effects of the drug on drug consumption by introducing a TO after injections. In this way, drug consumption under the present conditions was determined more exclusively by the reinforcing effect of the drug. It may be the case that drug consumption controlled exclusively by reinforcing effects does not conform to the UP model.

Other issues relevant to the behavioral economics model can be addressed when considering the present data. One question is whether the present data are best described as linear or nonlinear. Demand curves are typically characterized as positively decelerating curves (Bickel et al., 1990). At the lower UPs, the slope approximates zero, while at higher UPs consumption decreases at an increasing rate. Hursh (1991) derived an equation describing the positively decelerating nature of demand curves in which both the natural log and the raw metric of UP were included. In the present analysis, inclusion of the raw metric of UP did not significantly improve the fit of the model. On the other hand, in-

clusion of the raw metric of UP in the analysis of UP ratio slightly improved the fit, suggesting that a non-linear model using the UP ratio was a marginally better predictor of consumption than UP under the present conditions. It may be that the present data were primarily observed within the part of the demand curve which could be reasonably represented by a linear relationship. If lower UPs had been tested, it is more likely that the non-linear relationship would have been observed. Multiplying the ratios by the sum of the UPs for cocaine and food increased the amount of variability accounted for by the model. Furthermore, omitting low-dose data from the UP analysis improved the fit. Although the theoretical basis for either manipulation is unclear, this finding is consistent with results of other experiments (see Bickel et al., 1993). It remains for future research to address these issues.

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