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Dose and Elasticity of Demand for Self-administered Cocaine in Rats

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Abstract

The present experiment tested whether the elasticity of demand for self-administered cocaine in rats is dose-dependent. Subjects lever pressed for three different doses of intravenous cocaine – 0.11, 0.33, and 1.0 mg/kg/infusion – on a demand procedure where the number of lever presses required per infusion increased within a session. The main finding was that demand for the 0.11 mg/kg dose was more elastic than it was for the two larger doses. There was no difference in demand elasticity between the 0.33 and 1.0 mg/kg doses. These results parallel findings previously reported in monkeys. The present study also demonstrated that a within-session procedure can be used to generate reliable demand curves.

Keywords

demand; elasticity; essential value; cocaine; self-administration; rats

Introduction

A number of studies investigating drug reinforcers have used Hursh and Silberberg's (2008) exponential demand model to quantify reinforcer value (e.g., Bentzley et al., 2013; Galuska et al., 2011; Koffanus & Woods, 2013). This model provides a single number – α – that quantifies the essential value of a reinforcer. Reinforcers for which demand is relatively inelastic have higher essential value (and smaller α) than reinforcers for which demand is more elastic.

The model assumes that essential value is independent of reinforcer magnitude. Hursh and Silberberg (2008) found that this assumption was supported when they applied their model to rats' responding for varying magnitudes of food or doses of the opiate alfentanil. For example, in a study by Ko et al. (2002), rats self-administered 4 different doses of alfentanil over a range of fixed-ratio (FR) schedules. Although the numbers of infusions self-administered varied across doses, α was constant, demonstrating that the essential value of alfentanil was dose-independent.

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Conflicts of interest: None

There is, however, evidence suggesting that the essential value of cocaine is not always dose-independent. Hursh and Winger (1995) found that monkeys' demand for a small, reinforcing cocaine dose (0.01 mg/kg) was more elastic than it was for larger doses (0.03 and 0.1 mg/kg). Winger et al. (2006) corroborated this observation in another study with monkeys. These results suggest that small cocaine doses qualitatively differ from large doses in reinforcing effectiveness. Results from choice studies are consistent with this conclusion (Nader et al., 1993; Woolverton et al., 1997).

The primary goal of the present experiment was to test in rats whether the essential value of cocaine depends on dose, as it does in monkeys. Recently, there has been increased use of small doses (~0.1 mg/kg/infusion) in rat self-administration studies (e.g., Beckmann et al., 2012; Eagle et al., 2015; Koffarnus & Woods, 2013). It is important to know how such small doses compare as reinforcers to larger doses. A secondary goal was to evaluate the viability of a within-session demand curve procedure. In previous studies (e.g., Christensen et al., 2008), the FR was manipulated across blocks of sessions, necessitating a large amount of training to obtain a demand curve. The ability to generate a demand curve within a single session could accelerate the pace of data collection.

Methods

Subjects

Fifteen adult male Long-Evans rats began the experiment. Four were removed due to catheter failure ($n = 3$) or illness ($n = 1$). Rats served in a previous, unrelated self-administration experiment. Thus, they already had intravenous catheters (see Kearns et al., 2012, for surgical details). Rats were individually housed in plastic bins and were maintained at 85% of free-feeding weight. Sessions occurred 5 days/week during the light phase. Procedures were approved by American University's IACUC.

Apparatus

Six operant chambers were used. Each was equipped with a response lever, syringe pump, and a fluid swivel/tether. Cocaine (2.56 mg/ml) was infused at a 3.19 ml/min rate. Dose was controlled by varying the duration of pump operation.

Procedure

Demand curves were generated for three doses of i.v. cocaine: 0.11, 0.33, and 1.0 mg/kg/infusion. Rats were tested with all doses in a within-subjects design. To counterbalance dose order, two or three rats were assigned to each of the six possible orders. For each dose, subjects were first trained on an FR-1 schedule of lever pressing during 2-h sessions. Rats were trained on this schedule for a minimum of three sessions and until the number of infusions self-administered did not vary by more than 10% across two consecutive sessions.

Rats were then tested for two 2.5-h demand sessions. The FR increased over successive 30-min blocks according to the sequence 1, 3, 10, 32, 56. After completing testing with one dose, subjects repeated the same sequence of FR-1 training and testing with the other two doses.

Data Analysis

The number of infusions self-administered at each FR was averaged across the two tests at each dose and expressed as mg/kg cocaine consumed. These data were fit by Hursh and Silberberg's (2008) exponential demand equation:

$$\log Q = \log Q_0 + k(e^{-\alpha Q_0 C} - 1),$$

where Q is quantity consumed, Q_0 is consumption as price approaches 0, k is a constant defining consumption range in log units ($k = 1.7$ here), α determines the rate of decline in consumption, and C is cost (FR value).

Repeated-measures ANOVAs and paired-samples t-tests compared numbers of infusions self-administered, mg/kg consumed, and α across doses. Following Winger et al. (2006), extra sum-of-squares F-tests determined whether the best-fit values for demand curve parameters significantly differed over doses. The null hypothesis was that parameters did not differ and therefore a single demand curve fit the data from different doses. A significant F-statistic indicated that a single demand curve could not accommodate data from different doses.

Results

Rats required means of $4.2 (\pm 0.7 \text{ SEM})$, $3.7 (\pm 0.4)$, and $4.3 (\pm 0.4)$ sessions with the 0.11, 0.33, and 1.0 mg/kg doses, respectively, to meet the FR-1 stability criterion prior to testing. Figure 1 presents results from the demand tests in three ways. The top panel shows that the number of infusions self-administered decreased as FR and dose increased. A 5×3 (FR $\times$ Dose) repeated-measures ANOVA confirmed significant effects of FR ($F[4,40] = 146.5, p < 0.001$), Dose ($F[2,20] = 19.3, p < 0.001$), and their interaction ($F[8,80] = 33.0, p < 0.001$). Collapsed across FR, the number of infusions self-administered at 0.11 mg/kg/infusion was greater than that at 0.33 mg/kg/infusion which was greater than that self-administered at 1.0 mg/kg/infusion (all $t[10]s \geq 3.0$, all $ps \leq 0.02$).

The middle panel of Fig. 1 shows cocaine consumption (mg/kg). Rats consumed approximately equal amounts of cocaine at 0.33 and 1.0 mg/kg/infusion across FRs by self-administering approximately three times as many 0.33 mg/kg infusions as they did 1.0 mg/kg infusions. In contrast, rats' cocaine intake at 0.11 mg/kg/infusion was about half that of the two higher doses. A 5×3 (FR $\times$ Dose) repeated-measures ANOVA indicated significant effects of FR ($F[4,40] = 283.2, p < 0.001$), Dose ($F[2,20] = 24.8, p < 0.001$), and their interaction ($F[8,80] = 6.6, p < 0.001$). Collapsed across FRs, rats consumed significantly less cocaine at 0.11 mg/kg/infusion than at the two higher doses (both $t[10]s \geq 5.2, p < 0.001$), which did not differ significantly ($t[10] = 1.8, NS$).

The bottom panel of Fig. 1 presents normalized demand curves fit to the mean consumption data using the exponential model. Consumption is expressed as a percentage of Q_0 , the consumption level expected as price approaches 0. The normalized price is the number of responses required at a particular FR to obtain 1% of Q_0 [(FR $\times$ Q_0)/100]. The main finding was that consumption decreased with increasing price more quickly for the 0.11 mg/kg dose

than it did for the other doses. The extra sum-of-squares F -test confirmed that while best-fit parameters did not significantly differ for the two larger doses ($F < 1$), a global fit could not accommodate the 0.11 dose ($F[4,9] = 8.9, p < 0.005$). Furthermore, a repeated-measures ANOVA indicated that α significantly differed over doses ($F[2,20] = 12.3, p < 0.001$). Subsequent paired-samples t -tests confirmed that α was significantly higher for the 0.11 mg/kg dose than for the other doses (both $t[10]s \geq 3.2$, both $ps < 0.01$), but did not differ significantly between the 0.33 and 1.0 mg/kg doses ($t[10] = 1.9, NS$).

During demand testing, the first ratio was always FR-1. This may have allowed rats to load up on cocaine early in the session. Such loading could have influenced the shape of the demand function. To investigate this, demand curves were refitted with first-hour consumption removed (i.e., excluding data from FR-3 and FR-10). The resulting values of α for each dose were essentially unchanged. They were originally 0.0071, 0.0023, and 0.0019 for the low, middle, and high doses, respectively. Excluding the first-hour, they were 0.0076, 0.0022, and 0.0018. An extra sum-of-squares F -test again indicated that while best-fit parameters did not significantly differ for the two larger doses ($F[2,2] = 2.1, NS$), a global fit could not accommodate the 0.11 mg/kg dose ($F[4,3] = 11.0, p < 0.05$). Model fits slightly improved when first-hour data were removed ($R^2 = 0.93, 0.98$, and 0.98 for the low, middle, and high doses, respectively).

Discussion

The present experiment shows that, for rats, a small cocaine dose had lower essential value than larger doses. Importantly, the essential values of the two higher doses tested (0.33 and 1.0 mg/kg) did not differ, even though these doses produced an approximately three-fold difference in numbers of infusions self-administered. These results replicate findings in monkeys (Hursh & Winger, 1995; Winger et al., 2006).

The present experiment showed that a within-session procedure can generate orderly demand curves. The exponential model accounted for >90% of the variance in consumption data. This compares well with between-session procedures where the model has been used (Christensen et al., 2008). Bentzley et al. (2013) recently developed a within-session demand procedure where price is manipulated by varying reinforcer magnitude (i.e., dose), rather than reinforcer cost (i.e., FR). The current within-session procedure is more similar to traditional demand procedures, where price is manipulated by varying cost.

A within-session demand procedure could be useful for investigators testing the effects of short-lasting manipulations (e.g., pharmacological interventions) on reinforcer value. Progressive-ratio (PR) schedules have previously been used in such situations. An advantage of the current procedure is that consumption is measured at different prices, thereby permitting economic demand analyses, whereas typically only one reinforcer is obtained at each ratio on a PR schedule. Behavioral economic measures obtained from demand curves can be more sensitive measures of reinforcer value than PR breakpoints (e.g., Panlilio et al., 2013).

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Figure 1.

The top panel presents the mean (+ SEM) numbers of infusions self-administered at each fixed-ratio (FR) value for each dose tested. The results presented are the average of the two within-session demand tests. The middle panel presents these results expressed in terms of mg/kg consumed. The bottom panel presents the same results as log-log normalized demand curves, where consumption is expressed as a percentage of Q_0 , the expected amount consumed as price approaches 0, and price is expressed as the number of responses required at a particular FR value to produce 1% of Q_0 [that is, normalized price = $(FR \times Q_0)/100$].

Hursh and Silberberg's (2008) exponential demand model was used to fit curves to the data from each dose. Values of α and R^2 are presented for each of the curves.

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