Behavioral Economic Assessment of Price and Cocaine Consumption Following Self-Administration Histories that Produce Escalation of Either Final Ratios or Intake

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Various self-administration procedures are being developed to model specific aspects of the addiction process. For example, 'increased cocaine intake over time' has been modeled by providing long access (LgA) to cocaine during daily self-administration sessions under a fixed-ratio (FR1) reinforcement schedule. In addition, 'increased time and energy devoted to acquire cocaine' has been modeled by providing access to cocaine during daily self-administration sessions under a progressive-ratio (PR) schedule. To investigate the distinctiveness of these models, the behavioral economics variables of consumption and price were applied to cocaine self-administration data. To assess changes in consumption and price, cocaine self-administration was tested across a descending series of doses (0.237–0.001 mg per injection) under an FR1 reinforcement schedule to measure drug intake in the high dose range and thresholds in the low range. Cocaine consumption remained relatively stable across doses until a threshold was reached, at which maximal responding was observed. It was found that a history of LgA training produced an increase in cocaine consumption; whereas a history of PR training produced an increase in the maximal price (P_{max}) expended for cocaine. Importantly, the concepts of consumption and price were found to be dissociable. That is, LgA training produced an increase in consumption but a decrease in P_{max}, whereas PR training produced an increase in P_{max} without increasing consumption. These results suggest that distinct aspects of the addiction process can be parsed using self-administration models, thereby facilitating the investigation of specific neurobiological adaptations that occur through the addiction process.
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INTRODUCTION

A number of investigators are developing self-administration procedures to model specific aspects of the cocaine addiction process. The current *Diagnostic and Statistical Manual of Mental Disorder* (DSM-IV; American Psychiatric Association, 2000) describes many different symptoms associated with drug dependence in general and cocaine dependence in particular. Some of these might be difficult to model in rats—such as 'unsuccessful attempts to reduce drug use' or 'abandonment of social or occupational activities'—however other features have been successfully addressed. For example, a growing literature has focused on relapse, which seeks to understand how environmental or interoceptive events cause drug-seeking (see reviews, Lu *et al*, 2004; Schmidt *et al*, 2005; Epstein *et al*, 2006). Others have focused on continued drug taking in the face of adverse consequences (Deroche-Gamonet *et al*, 2004;

Vanderschuren and Everitt, 2004) or changes in attention or impulsivity after extended cocaine intake (Dalley *et al*, 2005; Perry and Carroll, 2008). Each of these approaches has demonstrated that addiction-like symptoms change over time.

Two aspects that appear to be fundamental to the addiction process are 'increased intake over time' and 'increased time and energy devoted to acquiring the drug' (DSM-IV). In behavioral economic terms, the first aspect is concerned with consumption whereas the second is concerned with price (ie effort expended). Increased cocaine intake over time has been clearly demonstrated by Ahmed and Koob (1998). This highly cited work has taken advantage of the fact that access to cocaine on a fixed-ratio 1 (FR1) reinforcement schedule during relatively long daily self-administration sessions (eg 6 h/day) results in an increased rate of drug intake after multiple sessions (Ahmed and Koob, 1998, 1999). A second aspect that focuses on increases in time and energy devoted to acquiring the drug has been explored using a progressive-ratio (PR) schedule. Depending on the unit injection dose and speed of injection, the behavioral cost an animal might pay for a cocaine injection can dramatically increase with time (Liu *et al*, 2005b; Morgan *et al*, 2006). It remains unclear whether

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self-administration histories that produce changes in consumption necessarily result in changes in maximum price paid (cf Paterson and Markou, 2003; Liu *et al*, 2005a). The present study sought to examine the relationship between consumption and price using the two different cocaine self-administration histories that have been specifically designed to increase either drug intake or price paid for cocaine.

The procedure used here was adapted from a study by Zittel-Lazarini *et al* (2007) in which a descending series of unit injection doses were used to determine the threshold dose of cocaine. The concept of 'threshold' implies that there is a dose that is minimally effective in supporting self-administration behavior. However, in determining this threshold, it should be noted that animals must respond at very high rates on an FR1 reinforcement schedule to maintain a constant level of drug intake. For example, Zittel-Lazarini *et al* (2007) report that a cocaine dose as low as 8 µg per infusion can support stable patterns of responding, engendering rates as high as 251 responses per hour. It is likely, therefore, that the threshold determined on an FR1 reinforcement schedule must be influenced by the relatively high 'price' observed at very low doses. In fact, Zittel-Lazarini *et al* (2007) suggested that concepts of behavioral economics could be used to advantage in the analysis of threshold determinations. As the threshold procedure yields information concerning both consumption (at high doses), as well as a behavioral economic index of price (P_{max}), this procedure was used here to assess the consequences of self-administration histories suggested to model important aspects of the addiction process.

MATERIALS AND METHODS

Animals, Surgery, and Housing

Male Sprague–Dawley rats (Harlan, Indianapolis, IN, USA), weighing approximately 350 g at the start of each experiment, were used as subjects. Upon acquisition, 57 rats were used for these experiments. A primarily cannula-related attrition resulted in complete data being collected from 45 rats. Throughout the experiments, rats were maintained on a reverse 12 h light–dark cycle (lights on at 1500 hours) with food and water available *ad libitum*. Before the beginning of the study, rats were anesthetized with an i.p. injection of ketamine (100 mg/kg) and xylazine (8 mg/kg) and implanted with a chronically indwelling Silastic® cannula (CamCaths, Cambridgeshire, UK) into the right jugular vein. The cannula exited through the skin on the dorsal surface in the region of the scapulae (Roberts and Goeders, 1989). Animals were then housed individually in 30 × 30 × 30 cm experimental chambers. The cannula was connected with Tygon® tubing (through a stainless steel tether) to a counterbalanced fluid swivel (Instech Laboratories Inc., Plymouth Meeting, PA, USA) mounted above the chamber. The swivel was connected to an infusion pump (Razel Scientific Instruments Inc., Stamford, CT, USA). Cannulae were flushed daily with heparinized saline to help maintain patency. All experiments were approved by the Wake Forest University Institutional Animal Care and Use Committee.

General Self-Administration Methods

Following surgery, rats were allowed 3–5 days to recover before self-administration testing began. Self-administration sessions occurred 7 days per week, each beginning in the middle of the dark cycle. The start of a session was signaled by the extension of a lever into the experimental chamber. During acquisition and during FR and PR training sessions cocaine was infused as a bolus of about 0.1 ml of cocaine solution over approximately 4–5 s (adjusted according to body weight). Doses (0.75 and 1.5 mg/kg per infusion) were manipulated by adjusting the concentration of cocaine solution (2.5 and 5.0 mg/ml, respectively). Following each response the lever was retracted and a light was illuminated for a 20-s time-out period. During threshold testing the dose was manipulated by adjusting the pump duration as described below.

Acquisition Phase

During the acquisition phase all animals received access to cocaine (0.75 mg/kg per infusion) on an FR1 schedule of reinforcement during daily training sessions, which terminated after a maximum of 20 infusions or a period of 6 h had elapsed. An animal was considered to have acquired stable self-administration if 20 injections were self-administered during a single session and the pattern displayed consistent post-infusion pauses between each of the injections.

Test Group Used to Demonstrate Threshold Procedure and Analysis

One group of rats ($n = 8$) was used to demonstrate proof-of-principle of the threshold procedure and data analyses. Following acquisition, animals were given access to cocaine (0.75 mg/kg per infusion) during 1 h sessions on an FR1 schedule of reinforcement for 14 consecutive days and then were tested using the threshold procedure describe below.

Cocaine Self-Administration Threshold Procedure

Rats were tested through a descending series of unit injection doses reinforced on an FR1 reinforcement schedule during daily 2 h sessions. Threshold was defined as the lowest dose that maintained daily intake. The dose was manipulated by holding the concentration of the drug constant and manipulating the pump duration. Pump times were decreased each day along a quarter-log scale as follows: 3156, 1780, 1000, 562, 310, 178, 100, 56, 31, 18, and 10 ms. A time-out period corresponded only to the duration of the pump infusion. The calculated dose equivalents (5 mg/ml × 1.6 ml/min × pump duration) are as follows: 421, 237, 133, 75, 41, 24, 13, 7.5, 4.1, 2.4, and 1.3 µg per infusion. These provided unit-doses corresponding to doses of (1120, 630, 350, 200, 110, 60, 30, 20, 10, 5, and 3 µg/kg per infusion) for a rat weighing 375 g. Only the final 10 unit-doses were used for group comparisons. It should also be noted that no significant differences in body weight were observed between groups.

An important consideration is whether turning an infusion pump on for only a few milliseconds is sufficient to deliver any amount of drug. This issue is addressed in the Supplementary Information (S1). The computer logged the cumulative pump durations across the sessions and drug volumes were recorded by the experimenter before and after each session. It was verified that intermittent delivery—even at very short intervals—resulted in the appropriate total volume of drug being delivered. The correlation (r) between expected and actual drug delivered by this method was 0.98.

Behavioral Economics

P_{max}, defined as the unit-price at which maximal responding occurs (Hursh, 1991), can be determined two ways. A common method used to determine P_{max} involves calculating the unit-price at which maximal responding occurs on a demand curve (Hursh, 1991; Campbell et al, 1999; Cosgrove and Carroll, 2002). Individual demand curves were obtained by graphing daily intake (total drug in mg per 2 h session) as a function of unit-price (FR1/unit dose). P_{max} values were first calculated by analyzing the point at which the slope of a demand curve became elastic, which theoretically represents the point at which maximal responding occurs (Hursh, 1991). Calculated P_{max} values and representative demand curves that were curve-fitted using equations described in greater detail by Hursh and Silberberg (2008) are demonstrated in the Supplementary Information (S2). P_{max} can also be determined graphically by measuring the unit-price at which maximal responding occurs by plotting daily responding as a function of unit-price (Greenwald and Hursh, 2006; Lenoir and Ahmed, 2008). The apex of the price–response function (white circles, Figure 1c) was used to determine P_{max}. The relationship between P_{max} values calculated using a demand curve analysis and P_{max} values that were graphically determined is demonstrated in the Supplementary Information (S2) and further described in the Results section. All P_{max} values reported in the current study were determined graphically from individual animals, as demonstrated in Figure 1c.

Long-Access and Short-Access Training

Two groups of animals were used for this experiment. Animals in the long-access group (LgA; $n = 8$) were given access to cocaine (0.75 mg/kg per infusion) on an FR1 schedule of reinforcement during daily 6-h sessions for 14 consecutive days. Previous reports indicate that animals increase, or 'escalate,' cocaine intake over 14 days under LgA conditions (Ahmed and Koob, 1998, 1999). Animals in the short-access group (ShA; $n = 6$) were given access to cocaine (0.75 mg/kg per infusion) on an FR1 schedule of reinforcement for 14 consecutive days during 2-h sessions. It has previously been reported that 3 h of access or less does not result in an escalation of cocaine intake across days (Wee et al, 2007). After completion of 14 days with either short- or long-access conditions, the two groups entered the threshold procedure. The independent variable in this experiment was the exposure to a pharmacological history of long vs short access to cocaine.
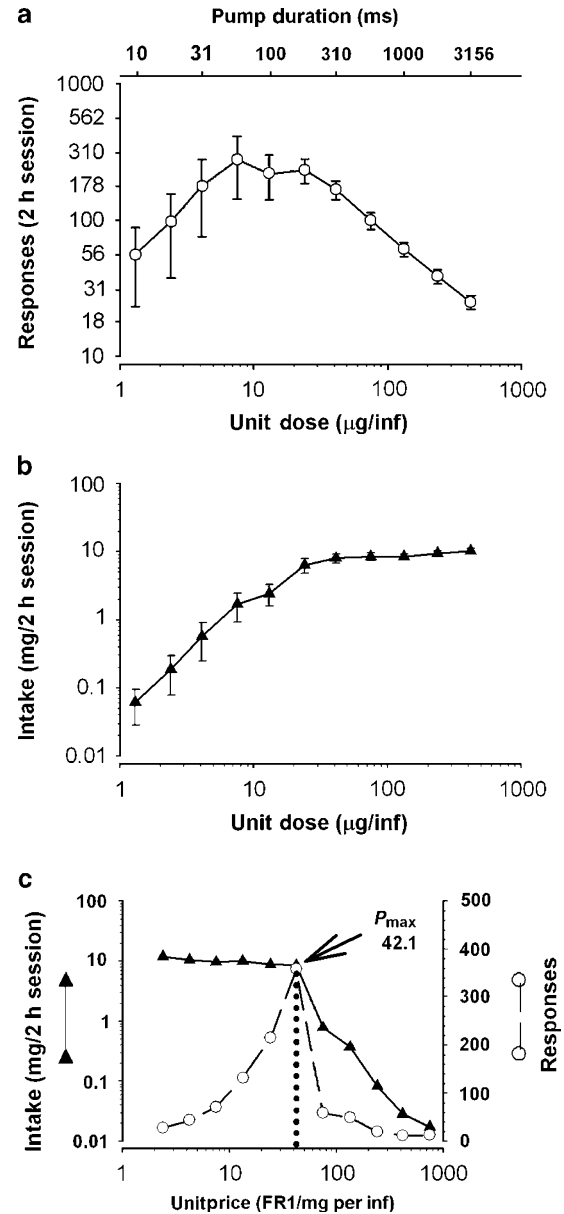

Figure 1 Dose–effect and price–effect relationships derived from self-administration data using a threshold procedure. (a) Dose–response relationship from a group of animals ($n = 8$) tested through a descending series of unit injection doses of cocaine during daily 2 h sessions. The dose of cocaine was reduced each day by adjusting the pump duration (top x-axis); the corresponding unit injection dose is shown on the bottom x-axis. Data are expressed as mean ($\pm$ SEM) responses on a fixed-ratio (FR1) schedule. (b) The dose–intake relationship demonstrates that a relatively stable level of cocaine intake is maintained at the high end of the dose range. Data are expressed as mean ($\pm$ SEM) daily intake. (c) An individual animal's P_{max} (maximal price) is graphically determined. The animal's daily responses (right y-axis) and intake (left y-axis) are both plotted as a function of unit price (FR1/unit dose). The unit price at which maximal responding occurs (P_{max}), which is graphically distinguishable as the apex of the price–response function (white circles), coincides with the point before which daily intake (black triangles) rapidly declines in response to an increase in price.

Progressive-Ratio Responding and Matched Intake

Two groups of animals were used for this experiment. Animals in the PR group ($n = 8$) were given access to cocaine (1.5 mg/kg per infusion) on a PR schedule of

reinforcement for 14 consecutive days during 6-h sessions. Under this PR schedule, delivery of i.v. cocaine injections (1.5 mg/kg per infusion) was contingent upon an increasing number of responses incremented through the following progression: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603 (Richardson and Roberts, 1996). Final ratios were defined as the response requirement corresponding to the final drug infusion. Although, the session duration was 6 h, animals typically reached the final ratio within 3 h. Previous reports have shown that with this dose of cocaine final ratios increase across days (Liu *et al*, 2005b; Morgan *et al*, 2006). A matched-intake group (Match; $n = 7$) was given access to cocaine (1.5 mg/kg per infusion) on an FR1 schedule of reinforcement for 14 consecutive days. The total number of injections available during each daily session corresponded to the mean number of daily infusions self-administered by the PR group, which gradually changed over days. The number of daily infusions was adjusted across days as follows (12, 14, 15, 14, 15, 16, 15, 18, 17, 17, 17, 18, 17, and 18). It should be noted that one animal from the Match cohort was excluded because of the observation that the animal's mean data fell three standard deviations away from the group mean. Upon completion of training these two groups entered the threshold procedure. The independent variable in this experiment was the exposure to a behavioral history of responding on a PR schedule.

Drug

Cocaine HCl, obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC, USA), was dissolved in a solution of sterilized 0.9% saline. The cocaine solution (5 mg/ml) was passed through a microfilter (0.45 μm pore size).

Statistics

All statistics were performed using SigmaPlot (version 11). All dose–intake comparisons were performed using a repeated-measures ANOVA with Holm–Sidak *post hoc* analyses. All P_{max} and individual dose comparisons were performed using Student's *t*-tests. Correlations are reported as a Pearson's *r*.

RESULTS

Figure 1 illustrates the dose–response and dose–intake curves as well as a representative graph illustrating how the P_{max} value was derived using the threshold procedure. Figure 1a shows the dose–response curve for a group of animals ($n = 8$; test group used to demonstrate threshold procedure and analyses) that self-administered cocaine through a descending series of 11 unit injection doses on an FR1 reinforcement schedule. Note that each pump duration (top *x*-axis) corresponds to a unit-dose (bottom *x*-axis) as described in greater detail in the Materials and Methods section (see cocaine self-administration threshold procedure). This method of data presentation, which is commonly used to depict the dose–effect relationship, shows an apparent ascending and descending limb. The same data are plotted in terms of dose *vs* intake (Figure 1b) to

demonstrate that a relatively constant level of cocaine is maintained at the upper end of the dose range. Although the log–log coordinates emphasize that intake is relatively stable at high doses before rapidly declining at some point, it should be noted that intake is actually gradually declining in response to decreases in the available unit-dose. However, it is not clear from either Figure 1a or b which, point corresponds to the threshold dose that maintains a maximal rate of responding before intake rapidly declines.

An individual animal's daily response (right *y*-axis) and intake (left *y*-axis) data, both plotted as a function of unit-price, are illustrated in Figure 1c. Note that the *x*-axis is transposed—relative to 1a and b—so that the lowest doses appear on the right, to represent the higher work cost required to maintain a relative level of cocaine intake at the low doses. The unit-price at which maximal responding occurs (P_{max}), which is graphically distinguishable as the apex of the price–response function (white circles), coincides with the point at which daily intake (black triangles) rapidly falls off in response to an increase in price. The unit-price at which maximal responding occurs before intake rapidly decreases, or demand becomes elastic, can also be calculated from a demand function as demonstrated in the Supplementary Information (S2). P_{max} values were first calculated using equations analyzing the slopes of individual demand curves (see S2). However, as previously reported by Greenwald and Hursh (2006), no significant difference was found between P_{max} values calculated from demand curve analyses and graphically determined P_{max} values ($t_{(7)} = -0.059$, NS; Supplementary Information S2). In addition, a high correlation was found between the calculated and graphically determined P_{max} values reported in the Supplementary Information ($r = 0.99$).

Representative cumulative records from the threshold procedure are illustrated in Figure 2. Figure 2a shows cumulative records from one animal used in Figure 1 (ie the test group used to demonstrate threshold procedure and analyses) responding at the 41 μg per infusion dose (i), the 24 μg per infusion dose (ii), and the 13 μg per infusion dose (iii). These cumulative records demonstrate responding at a suprathreshold dose (i), a threshold dose (ii), and a subthreshold dose (iii).

The results of LgA and ShA training on responding for cocaine over 10 doses are illustrated in Figure 3. Figure 3a shows the escalation of cocaine-reinforced responding across sessions observed in animals given access to cocaine for 6 h per day (LgA), in comparison to the relatively constant responding across sessions in animals given access to cocaine for 2 h per day (ShA). As expected, the LgA training procedure resulted in a significant increase in responding across 14 sessions ($F_{(13, 91)} = 6.794$, $p < 0.01$). Figure 3b shows cocaine intake as a function of dose between the LgA and ShA groups. Repeated-measures ANOVA revealed a significant effect of Dose ($F_{(9, 108)} = 67.0$, $p < 0.001$), no significant effect of Group ($F < 1$), and a significant Dose × Group interaction ($F_{(9, 108)} = 7.2$, $p < 0.001$). Holm–Sidak *post hoc* analysis revealed the LgA group consumed significantly more cocaine at two higher doses (237 μg per infusion: $t_{(12)} = 2.85$, $p < 0.05$; 133 μg per infusion: $t_{(12)} = 2.80$,
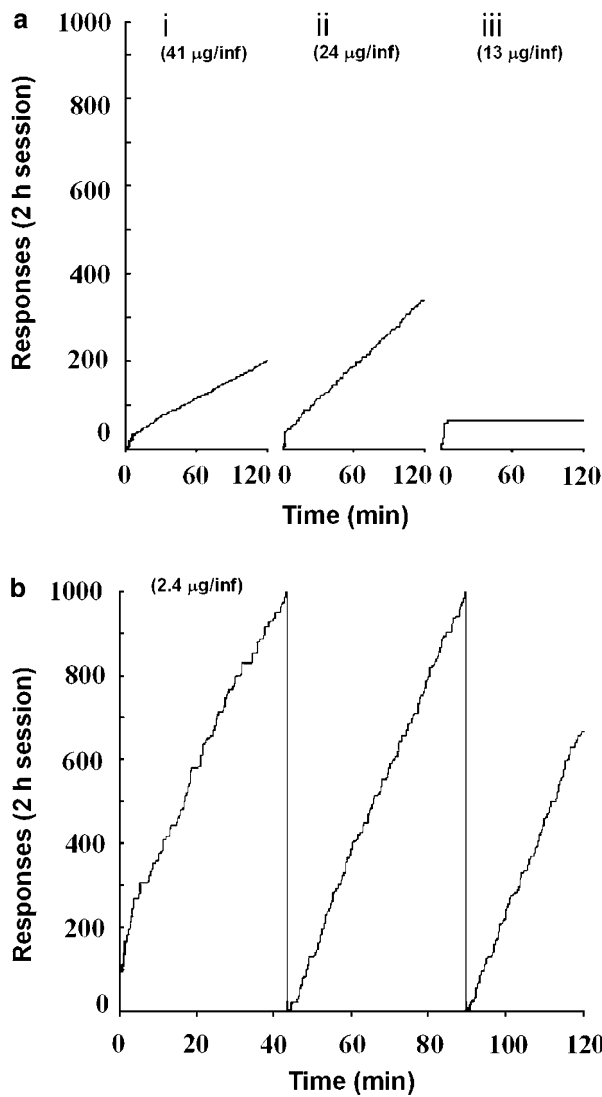
Figure 2 Cumulative records from the threshold procedure demonstrate supra-, threshold, and subthreshold responding. (a) Cumulative records from one animal responding at the 41 µg per infusion dose (i), the 24 µg per infusion dose (ii), and the 13 µg per infusion dose (iii) are shown. These cumulative records represent supra-, threshold, and subthreshold responding, respectively. Note that responding is maintained throughout the duration of the session in each cumulative record, except at the subthreshold dose (13 µg per infusion; iii). (b) A cumulative record from one animal from the progressive-ratio (PR) group responding at the 2.4 µg per infusion dose is shown. In this case, cocaine (2.4 µg per infusion) was found to sustain responding at a rate of 1334 responses per hour. Note that every 1000 responses the record of cumulative responses resets at zero.

$p < 0.05$) and significant less cocaine at a lower dose (24 µg per infusion: ($t_{(12)} = -2.98$, $p = 0.05$).

The results of a behavioral history of PR training on responding for cocaine over 10 doses are illustrated in Figure 4. Figure 4a shows the expected escalation of final ratios over 14 days ($F_{(13, 91)} = 2.892$, $p < 0.01$). Figure 4b shows cocaine intake as a function of dose between PR-trained animals and animals matched for intake and dose (Match). Repeated-measures ANOVA revealed a significant effect of Dose ($F_{(9, 108)} = 34.3$, $p < 0.001$), no significant effect of Group ($F < 1$), and a significant Dose × Group interaction
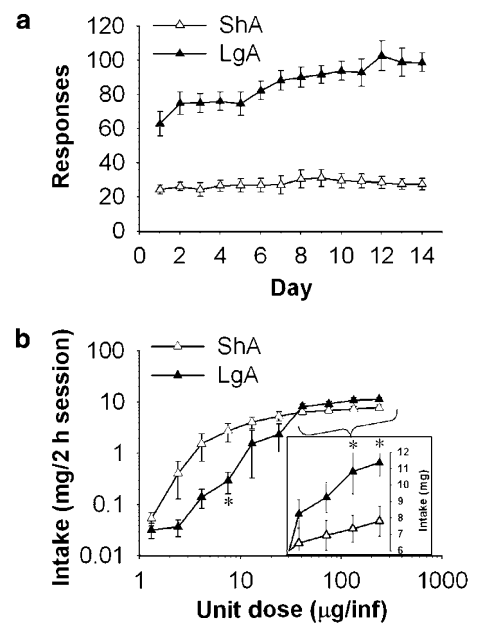

Figure 3 long-access (LgA) training results in an increase in cocaine consumption. (a) LgA training (black triangles) results in an increased rate of cocaine intake across daily 6-h sessions; whereas short-access (ShA) training (white triangles) results in stable responding across daily 2 h sessions. Data are expressed as mean (± SEM) daily responses on a fixed-ratio (FR1) schedule. (b) LgA trained animals (black triangles) consume more cocaine at the 237 and 133 µg per infusion doses and less cocaine at the 24 µg per infusion dose in comparison to the ShA group. Data are expressed as mean (± SEM) daily intake and asterisks indicate significant differences between groups ($p < 0.05$).
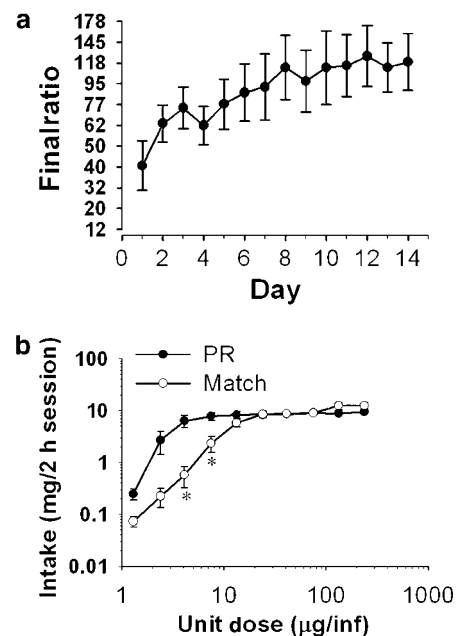

Figure 4 Progressive-ratio (PR) training increases the reinforcing strength of cocaine. (a) PR training (black circles) results in increased final ratios across daily sessions. Data are expressed as the mean (± SEM) final ratio. (b) PR-trained animals (black circles) consume more cocaine at the 4.1 and 7.5 µg per infusion doses in comparison to the Match group. Data are expressed as mean (± SEM) daily intake and asterisks indicate significant differences between groups ($p < 0.05$).
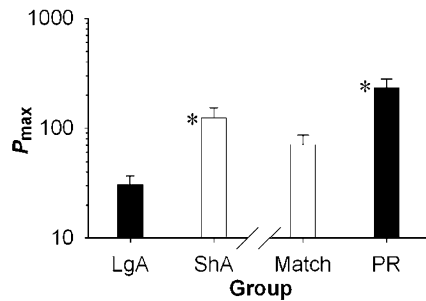
Figure 5 Effect of self-administration procedures that produce an escalation of consumption or final ratio on P_{max}. Data are expressed as the mean ($\pm$ SEM) P_{max}. The left pair of bars illustrates P_{max} values determined from animals that had been tested with access to cocaine during daily 6 h (long access, LgA) or 2 h (short access, ShA) sessions for 14 days. The right pair of bars illustrates P_{max} values from groups of animals that had been tested for 14 days on a progressive-ratio schedule (PR) or a fixed-ratio (FR1) schedule matched for total drug intake (Match). Asterisks indicate significant differences between groups ($p < 0.05$).

($F_{(9, 108)} = 5.8$, $p < 0.001$). Holm–Sidak *post hoc* analysis revealed the PR group consumed significantly more cocaine at two lower doses (7.5 μg per infusion: $t_{(12)} = 3.45$, $p < 0.05$; 4.1 μg per infusion: $t_{(12)} = 3.63$, $p < 0.05$) The mean rate of responding for the PR group at threshold (apex for the dose–response curve for each animal) was 955 responses per hour $\pm$ 244 (SEM). Figure 2b shows a cumulative record from one animal from the PR group responding at an extremely low dose of cocaine (2.4 μg per infusion dose). This record was chosen to illustrate that high rates of responding could be maintained throughout the 2 h session. In this case, cocaine was found to sustain responding at a rate of 1334 responses per hour.

The results of the behavioral economics variable P_{max} determined from each experimental group are illustrated in Figure 5. The left side of Figure 5 shows P_{max} values determined from the LgA and ShA groups. The LgA group is represented by black bars whereas the ShA group is represented by white bars. LgA-trained animals showed a significantly reduced P_{max} in comparison animals given ShA to cocaine ($F_{(1, 12)} = 12.417$, $p < 0.01$). The right side of Figure 5 shows P_{max} values determined from the PR group and the match group. The PR group is represented by black bars whereas the match group is represented by white bars. PR-trained animals exhibited a significantly increased P_{max} vs the match group ($F_{(1, 12)} = 8.33$, $p = 0.014$). P_{max} values and final ratios were also compared within the same animal. A correlation was found between P_{max} values established using the threshold procedure and final ratios established using a PR schedule ($r = 0.705$) as illustrated in the Supplementary Information (S3).

DISCUSSION

In the present study, cocaine self-administration was tested across a descending series of doses to assess threshold and rate of drug intake. Ten unit injection doses (237–1.3 μg per injection) were examined between groups so as to allow for the evaluation of drug intake rates in the high-dose range and thresholds in the low-dose range. This experimental approach was used to examine how two different behavioral histories of cocaine self-administration—each suggested to

model different aspects of the addiction process—affect the behavioral economic measures of price and consumption.

Consumption of cocaine on an FR1 reinforcement schedule appears to be tightly regulated. It has long been known that at suprathreshold doses the rate of self-injection is inversely related to unit injection dose (Pickens and Thompson, 1968; Wilson et al, 1971). Lower doses are self-administered more frequently than higher doses, thus resulting in hourly cocaine intake that remains relatively constant across a wide dose range. Figure 1b clearly shows that from 421 to 41 μg per infusion, total cocaine intake per 2 h session is relatively constant. Although there is some debate as to whether cocaine intake is controlled by satiety mechanisms alone (Tsibulsky and Norman, 1999; Lynch and Carroll, 2001), or whether avoidance of aversive/toxic consequences of high blood levels may also suppress responding (Pettit and Justice, 1989; Lynch and Carroll, 2001; Roberts and Zito, 1987; Ettenberg, 2004), it is commonly assumed that animals titrate their cocaine intake around some preferred blood or brain level (Tsibulsky and Norman, 1999; Lynch and Carroll, 2001; Ahmed and Koob, 2005; but see also Panlilio et al, 2003). The observation that animals alter response output to maintain cocaine intake has led to theories suggesting that self-administration continues until intake falls below a set point (Ahmed and Koob, 1998), trigger point (Wise et al, 1995), or satiety threshold (Tsibulsky and Norman, 1999).

At some point in the descending series of doses, responding sharply declines. The lowest dose that maintains consistent intake is defined as the threshold. It is important to note that as the suprathreshold dose approaches the threshold, animals must respond at very high rates to maintain a relatively constant level of drug intake. Figure 2b shows a remarkable example of an animal responding on the lever more that 2600 times during a 2 h session, reinforced by an exceedingly small dose of cocaine (2.4 μg per injection). Clearly this animal is expending considerable time and energy in 'defending' a particular drug level, and this response cost must necessarily be an important factor influencing responding near threshold. Behavioral economics provides a theoretical framework that can be used to examine data from threshold determinations for information concerning both price and consumption.

Central to behavioral economic analysis is unit-price, which is defined as the response requirement per unit injection dose (mg per infusion). As unit-price is a ratio, it can be altered by changing either the response requirement (numerator) or the dose (denominator); either way, the theoretical issues influencing unit-price remain the same (Bickel et al, 1990, 1993). Altering unit-price is more commonly accomplished by changing the FR requirement or by using a PR schedule (Cosgrove and Carroll, 2002; Wade-Galuska et al, 2007; Lenoir and Ahmed, 2008). Manipulating the dose and holding the response requirement constant (eg FR1) is also a valid method as illustrated by Zittel-Lazarini et al (2007) and the present study. Analysis of the unit-price data yields P_{max}, which is defined as the unit-price at which maximum responding occurs (Hursh, 1991).

P_{max} and final ratio have been suggested to measure similar aspects of reinforcement strength (Rodefer and Carroll, 1997; Cosgrove and Carroll, 2002). However, it was

not clear if P_{max} values established using threshold determinations would correlate with final ratios established at high doses. Obviously differences in dose, frequency of drug delivery, and fluctuations in blood/brain levels may influence P_{max} and final ratio differently. This prompted us to examine the relationship between P_{max} and final ratio within the same animal. We found a correlation between P_{max} and final ratio as illustrated in the Supplementary Information S3 ($r = 0.705$), suggesting a relatively strong relationship between P_{max} established from threshold determinations and final ratios established at a high dose (1.5 mg/kg per infusion) of cocaine. These data suggest that threshold determinations may provide information pertaining to some aspect of reinforcement strength.

A behavioral economic analysis was used here to assess changes in P_{max} and consumption following behavioral histories suggested to model different aspects of the addiction process. Ahmed and Koob (1998, 1999) have shown that consumption of cocaine increases across sessions if animals are given extended access to cocaine during daily 6 h sessions in comparison to animals that are given short access. This robust effect was replicated here; animals given daily 6 h access (LgA) to cocaine on an FR1 reinforcement schedule showed a clear escalation in cocaine intake (Figure 3a). Previous reports have shown that the animals exhibiting increased responding at the 250 μg per infusion dose also show increased responding at lower doses 250–31.25 μg per infusion (Ahmed and Koob, 1998, 1999). Here we extended this analysis through a series of 10 unit doses. As expected, the LgA group showed significantly higher intake in the upper end of the dose range. By contrast, however, inspection of Figure 3b shows that intake was reduced at the lower end of the dose range compared to the ShA group. In effect, the LgA group reached a threshold at a higher dose in comparison to ShA animals (Figure 3c). A behavioral economic analysis revealed that the LgA group showed a significantly lower P_{max} than the ShA group. We interpret the observations that LgA escalation training produces animals exhibiting increased consumption of cocaine at high doses, but a diminished reinforcing effectiveness of low doses, to be indicative of the development of tolerance to the reinforcing effects of cocaine. According to the DSM-IV the development of tolerance, defined by either a need for markedly increased amounts of the substance to achieve intoxication or desired effects, or markedly diminished effects with continued use of the same amount of the substance, is an important component of the addiction process. We wish to emphasize that the LgA model, which produces an increase in cocaine consumption, captures a fundamental aspect of the addiction process.

We also examined a procedure that models a different aspect of cocaine addiction, ie 'increased time and energy devoted to acquiring the drug.' Animals given the opportunity to self-administer cocaine on a PR schedule demonstrate increased final ratios over time. This effect is dose dependent (1.5 mg/kg per injection being the optimum dose), and is only seen with rapid drug infusions, suggesting that speed of drug onset is an important variable (Liu *et al*, 2005b; Morgan *et al*, 2006). In the current study, we replicate the finding that final ratios escalate across daily PR sessions (Figure 4a) and extend the analysis to an examination of consumption and P_{max}. Here we show that

the PR group, which showed an escalation in final ratios, responded at higher rates in the lower dose range in comparison to animals that were matched for intake and dose during training (Figure 4b). That is, PR training produced animals that paid a higher behavioral price for low doses of cocaine *vs* comparative controls. Note that animals in the PR group escalated their final ratios when reinforced with a high dose of cocaine (1.5 mg/kg per injection). The observation that these animals show higher P_{max} values calculated from threshold doses suggests that the augmentation of the reinforcing effects extends across the entire dose range.

Some studies (Paterson and Markou, 2003; Allen *et al*, 2007; Wee *et al*, 2008) and theoretical arguments based on the concept of opponent processes (Ahmed and Koob, 2005; Ahmed, 2005) suggest that a history of increased consumption should result in an increase in the price expended for cocaine. For example, it has been reported that LgA to cocaine on an FR1 reinforcement schedule can result in an increase in final ratios on a PR schedule (Paterson and Markou, 2003, Allen *et al*, 2007; Wee *et al*, 2008). However, a great deal of evidence, including the data from the current study, suggests that the two phenomena can be dissociable. Liu *et al* (2005b) have demonstrated that LgA does not necessarily result in higher final ratios. In fact, in some circumstances, extended access to cocaine can prevent the increase in final ratios seen in the PR model (Morgan *et al*, 2006). In addition, treating animals with a high level of cocaine (18–20 mg/kg, i.v. every 8 h for 7 days) resulted in an increased rate of cocaine intake on an FR1 reinforcement schedule (Emmett-Oglesby and Lane, 1992; Emmett-Oglesby *et al*, 1993), but a decrease in the final ratio reached on a PR schedule (Li *et al*, 1994). These data lead us to conclude that a history of high cocaine consumption can be dissociated from an increase in the price an animal will expend for cocaine. Why, in some studies, high cocaine consumption can have a different effect on final ratios is presently unclear but may be related to factors such as strain differences, PR ratio requirements, housing conditions, and drug abstinence periods.

We have argued elsewhere (Roberts *et al*, 2007) that there are likely many different aspects to the addiction process, each with their own time course. The development of tolerance is thought to emerge late in the addiction process. For example, the DSM-IV suggests that the development of cocaine dependence occurs in sequential stages. Specifically, the early stages of cocaine addiction are considered to involve the development of an increased desire, or motivation, to take cocaine whenever it is available, whereas the later stages involve the development of tolerance to various effects of cocaine (DSM-IV, p 243). Indeed, we have shown that if animals are first exposed to procedures that increase final ratios on a PR schedule, this apparent increase in motivation to self-administer cocaine will survive periods of high drug intake (Morgan *et al*, 2006) that would normally produce tolerance to the reinforcing effects of cocaine. Thus, the paradox of why an addict might pay a high price for a drug that seems to have diminished reinforcing value might eventually be understood in the context of sequential addiction processes. The fact that 'price' and 'consumption' can be dissociated through procedures that address each process individually should

make the task of parsing the addiction process into its component parts somewhat easier.

DISCLOSURE/CONFLICT OF INTEREST

The authors have no related financial interests on considerations to disclose.

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