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The Effect of Nicotine Pre-exposure on Demand for Cocaine and Sucrose in Male Rats

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Abstract

The goal of the present study was to determine how nicotine pre-exposure affects the elasticity of demand for intravenous cocaine and for sucrose pellets in adult male rats. In Experiment 1, demand for cocaine was assessed in rats that had nicotine in their drinking water. Nicotine pre-exposure significantly decreased rats' willingness to defend cocaine consumption as price (measured as the number of responses per cocaine infusion) increased, compared to a control group with no nicotine pre-exposure. That is, nicotine increased the elasticity of demand for cocaine infusions. Experiment 2 repeated the first experiment, but with rats working for sucrose pellets instead of cocaine. Nicotine pre-exposure had no effect on the elasticity of demand for sucrose. This pattern of results suggests that nicotine preexposure can reduce the reinforcing effects of cocaine, but not sucrose, in adult male rats.

Keywords

demand; cocaine; nicotine; sucrose; rat

Introduction

Epidemiological studies suggest that the frequency of tobacco smoking covaries with cocaine use (Henningfield et al., 1990). For example, cocaine users are more likely to smoke cigarettes than non-cocaine users (Higgins et al., 1994), and those dependent on tobacco report an early age of onset for cocaine use (Budney et al., 1993). While it has often been thought that experience with nicotine causes increased cocaine taking, there also exists evidence that nicotine can decrease the subjective effects of cocaine in humans (Kouri et al., 2001). In their study, Kouri et al. provided participants with a nicotine-patch pretreatment before intranasal cocaine administration. They found higher visual analog scale scores for "High" and "Stimulated" responses to cocaine in subjects pretreated with placebo than in those pretreated with nicotine. Subjects pretreated with nicotine also took significantly longer to report the effects of cocaine and cocaine euphoria than subjects pretreated with placebo. Thus, there is evidence that the effects of cocaine may be attenuated by nicotine pretreatment in humans.

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Conflicts of interest

There are no conflicts of interest.

Animal studies investigating the effects of nicotine pretreatment on the reinforcing effects of cocaine have yielded mixed results. Levine et al. (2011) found that nicotine pretreatment increased the time that male mice spent in a cocaine-associated context in a conditioned place preference (CPP) test, a paradigm widely used to assess the rewarding and aversive effects of drugs. However, CPP involves processes other than reinforcement (e.g., Pavlovian conditioning, novelty seeking; Bardo and Bevins, 2000), making it difficult to discern the effects of nicotine on the reinforcing effects of cocaine specifically. Other studies have investigated the effect of nicotine pretreatment on cocaine self-administration in rats. It has been reported that nicotine acutely decreased rates of cocaine self-administration in male rats, whereas chronic pretreatment increased cocaine intake (Bechtholt and Mark, 2002). Another study found that chronic nicotine pretreatment facilitated the acquisition of cocaine self-administration in male rats, but did not alter asymptotic rates of cocaine taking (Horger et al., 1992). In a more recent study, Pomfrey et al. (2015) found no differences in cocaine self-administration between adult male rats that were pretreated with nicotine or vehicle in adolescence. In contrast to the results of Pomfrey et al. (2015), Reed and Izenwasser (2017) found that nicotine preexposure in adolescence, but not in adulthood, increased rates of cocaine self-administration in male rats after a 30-day nicotine-free period. These studies used rates of cocaine self-administration on fixed- or progressive-ratio schedules as the dependent measure.

The present study used demand analysis to investigate the effect of nicotine preexposure on cocaine-maintained behavior. Demand curves plot consumption of a good against its price, with price defined in rats as the amount of work (i.e., lever presses) needed to earn a reward. Typically, as price increases, demand decreases, resulting in a positively accelerated, monotonically decreasing function. Demand curves have a degree of elasticity, which describes how consumption changes with increases in price. If the rate of decrease in consumption exceeds the rate of price increase for the good, demand is said to be elastic. On the other hand, if consumption does not proportionally decrease with increases in price, demand is said to be inelastic. Demand for necessary goods, such as food, tends to be inelastic, whereas demand for luxury goods tends to be elastic (Hursh, 1980). The concept of elasticity has been used to index the essential value (Hursh and Silberberg, 2008) of different goods, such as drugs and food.

Hursh and Silberberg (2008) introduced the exponential model of demand to model demand curves:

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

In this equation Q is quantity consumed, Q_0 is consumption as price approaches 0, k is a constant defining the consumption range in log units, α determines the rate of decline in consumption, and C is cost (FR size). The parameter α describes the elasticity of the entire demand curve and is inversely related to a good's essential value.

Advantages of using a demand-curve analysis in self-administration studies include its multiple characterizations of drug demand at different prices, including demand at price

zero, and that it can precisely quantify the cost-benefit relationship of drug consumption (demand elasticity). This allows for a more complete characterization of a good's reinforcing properties than does a progressive-ratio (PR) schedule breakpoint. For example, Lamb and Daws (2013) compared different groups of mice that responded for ethanol reinforcers. They found that there were differences across groups in PR breakpoint. However, when they compared groups on elasticity of demand for ethanol (i.e., the essential value of ethanol), there were no differences. They concluded that the difference in PR breakpoint was due simply to differences in baseline ethanol consumption levels (i.e., corresponding to Q_0 from the equation above) and that the groups did not actually differ in how they valued the ethanol reinforcer [See also Panlilio et al. (2013) for another example of different results obtained with PR breakpoints vs. elasticity of demand]. The demand analysis used here inherently accounts for differences in baseline consumption and provides a single number reflecting changes in demand across the entire demand curve (Hursh and Silberberg, 2008; see also Bentzley et al., 2013 for discussion of the advantages of normalized demand analysis).

To date, no studies have investigated how nicotine pretreatment affects elasticity of demand for cocaine in rats. This absence is addressed in this report. Experiment 1 used behavioral economic techniques to assess the effect of nicotine preexposure on cocaine demand. Specifically, demand curves for cocaine were modeled using Equation 1 to assess how nicotine treatment history affected cocaine demand in adult male rats. In Experiment 2 we aimed to determine if nicotine generally affected motivation, or if effects were cocaine-specific. Experiment 2 tests this hypothesis by repeating Experiment 1, but measuring demand for sucrose pellets instead of cocaine.

Methods

Subjects

Eighteen naïve adult male Long-Evans rats served as subjects in Experiment 1. Twenty naïve adult male Long-Evans rats served as subjects in Experiment 2. All subjects were individually housed in plastic cages with wood-chip bedding, and given free access to food and water for the duration of the experiment. The rat colony had a 12-h light:dark cycle with lights on at 08:00 h. Training was conducted five days per week during the light phase of the light:dark cycle. Rats were treated in accordance with the Guide for the Care and Use of Laboratory Animals (National Academy of Science, 2011) and all procedures were approved by American University's Institutional Animal Care and Use Committee.

Apparatus

All training and testing was completed in six Med-Associates (St. Albans, VT) operant chambers ($30.5 \times 24 \times 29$ cm), enclosed in sound-attenuation chests. All chambers had front and rear aluminum walls, Plexiglas side walls, and a grid floor. Two Med-Associates retractable levers were positioned on the front wall of the chamber, 5 cm from the floor, equidistant from a food trough located in the center of the wall. Two cue lights (100-mA) were mounted to the front wall approximately 10 cm above the floor, and directly above each lever, and a tone stimulus (4000 Hz and 70 dB) was delivered through a speaker. A

house light (100-mA) mounted on the ceiling at the front of the chamber was illuminated to signal the start of a session and was extinguished to signal its end. In Experiment 1, Tygon tubing extended from 10-ml syringes to a 22-gauge rodent single-channel fluid swivel (Instech Laboratories, Plymouth Meeting, PA) and tether apparatus (Plastics One, Roanoke, VA) that descended through the ceiling of the chamber. Cocaine was delivered to the subject through this tubing, which passed through the metal spring of the tether apparatus. Cocaine (Drug Supply Program, National Institute on Drug Abuse, Bethesda, MD) in a saline solution at a concentration of 2.56 mg/ml was infused at a rate of 3.19 ml/min by 10-ml syringes driven by Med-Associates syringe pumps. In Experiment 2, in place of the cocaine self-administration equipment, boxes were equipped with a food-pellet dispenser that was used to dispense 45-mg banana-flavored sucrose pellets (Test Diets, Richmond, IN).

Nicotine Pre-exposure

Upon completion of the surgery in Experiment 1, or at the start of Experiment 2, rats were randomly assigned to the nicotine pre-exposure group (N), or the control group (C), with the restriction that half of the rats were assigned to each group. The N group was provided with water mixed with nicotine (15 mg/l) and saccharin (20 mg/l) as their sole water source. Doses are consistent with previous studies that use similar chronic nicotine pre-exposure protocols (Nesil et al., 2011). The C group was provided with water mixed with saccharin (20 mg/l). Both groups were given access to their respective water types for eight days before cocaine or food self-administration began. Their weights and water consumption were measured daily.

Experiment 1

Surgery—Before starting training on the behavioral procedures, all rats were surgically prepared with chronic indwelling jugular vein catheters, using procedures described in detail elsewhere (Thomsen and Caine, 2005; Tunstall and Kearns, 2014). Briefly, 3.5 cm of Silastic tubing was inserted into the right jugular vein. An additional 8 cm of tubing was passed under the skin to the midscalpular region, where it was attached to the 22-gauge stainless-steel tubing of a back mount catheter port (Plastics One, Roanoke, VA) that was implanted subcutaneously. All surgery was conducted under ketamine (60 mg/kg) and xylazine (10 mg/kg) anesthesia. Rats were given 3–5 days to recover from surgery before beginning nicotine pre-exposure. Catheters were flushed daily with 0.1 ml of a saline solution containing 1.25 µg/ml heparin and 0.08 mg/ml gentamicin.

Acquisition and Demand Procedure—Rats were first trained to lever press for cocaine on a fixed-ratio (FR)-1 schedule in once-daily 90-min sessions run at the same time each day. Rats had access to both an active and an inactive lever. A press on the active lever resulted in a 0.7 mg/kg infusion of cocaine and the simultaneous presentation of the tone and the cue light above the lever for 10 s. Presses on the inactive lever and all lever presses during the infusion and tone-light stimulus were recorded but had no consequence. To meet the stability criterion, rats had to self-administer a minimum of 12 infusions for three consecutive sessions, and obtain a minimum number of 60 total infusions. Subjects that did not reach criterion within 20 days were dropped from the study. Once subjects met the FR-1 acquisition criterion, the FR size increased each session according to the following

sequence: 3, 6, 12, 24, 48, 96, 192, 384. The sequence was ended early if the subject's number of infusions was less than 10% of what it had been at FR 1.

Experiment 2

Procedure—Acquisition and demand procedures were identical to those in Experiment 1 with the exception that sucrose pellets were used in place of cocaine. Rats were first trained to lever press for sucrose pellets on a FR-1 schedule in a 90-min session. To meet criterion, rats had to obtain a minimum of 12 sucrose pellets for three consecutive sessions, and a minimum number of 60 total sucrose reinforcers. There was an additional criterion of a five-session minimum, which was the minimum number of sessions in which a rat reached criterion in Experiment 1. Subjects that did not reach criterion within 15 days were dropped from the study. Once subjects met the FR-1 acquisition criterion, the FR size increased each session according to the following sequence: 3, 9, 27, 81, 243. This sequence was used instead of the more slowly progressing one used in Experiment 1 because previous studies have shown that rats complete larger ratios for food or saccharin than they do for cocaine (e.g., Christensen et al., 2008a; Kearns et al., 2016). Our goal was to capture the complete demand curve in a number of sessions similar to that used in Experiment 1. The sequence was ended early if a subject's number of infusions was less than 10% of what it had been at FR 1.

Data Analysis

To create the demand curves, the number of reinforcers earned was plotted against the price for reinforcers. The number of reinforcers earned at FR 1 was averaged over the last two sessions at FR 1. All other FR values were only used for one session. Group mean consumption data, as well as individual subjects' consumption data, were fitted with Equation 1, and the Q_0 and α values were determined. The primary measure of interest from the demand phases was essential value (EV). This was based on the model fits to the individual subjects' consumption data and was calculated according the formula given by Hursh (2014):

$$EV = 1/(100 * \alpha * k^{1.5}) \quad (2)$$

EV is inversely related to the α value, which describes elasticity of demand, and provides a measure of sensitivity to cost (Hursh, 2014). For example, higher EV reflects more inelastic demand, which indicates that the animal is willingly to work harder for a particular reward as its price increases. To facilitate comparison of demand elasticity across groups, normalized consumption was plotted as a function of normalized price (Christensen et al., 2008a). To normalize consumption, the number of cocaine infusions was expressed as percentage of Q_0 , the consumption level predicted by the model as price approaches zero. Price was normalized by converting it to the number of responses required at a particular FR to obtain 1% of Q_0 .

Results

Experiment 1

Seven N-group and six C-group rats completed the experiment. The other five rats were dropped due to loss of catheter patency. Only the data from rats that completed the study are included here. Figure 1A shows the percentage change in body weight from the baseline for each group over the duration of the study. A 2×2 repeated measures ANOVA indicated that body weight significantly increased over time ($F[4,60] = 58.68, p < .0001$). There was no effect of group on body weight ($F[1,60] = 1.48, NS$). Figure 1B shows the mean amount of liquid consumed by each group across the duration of the study. A 2×2 repeated measures ANOVA indicated that there was no significant difference in the amount of liquid consumed between groups ($F[1,44] = .24, NS$), although there was a significant main effect of time ($F[4,44] = 22.26, p < .0001$). Specifically, rats drank more during week one ($M = 50.61, SEM = 2.1$) than they did during weeks three ($M = 34.09, SEM = 1.7$), four ($M = 35.61, SEM = 2.5$), or five ($M = 35.05, SEM = 1.0$). Based on body weight and liquid consumption, the nicotine dose (mg/kg/day) was calculated. Figure 1C shows that across the 5 weeks of the experiment, rats consumed an average of 1.31 mg/kg/day ($SD = 0.2$).

Rats required a mean of $10.4 (\pm 1.3 \text{ SEM})$ sessions to reach the acquisition criterion on the FR-1 schedule of cocaine self-administration. There was no significant difference in the number of sessions required to meet criterion between the N and C groups (independent samples t -test: $t[11] = 0.88, NS$). Averaged over the final three FR-1 sessions, rats obtained a mean of $17 (\pm 0.8 \text{ SEM})$ cocaine infusions. There was no significant difference in the average number of infusions over these sessions between the N and C groups (independent samples t -test: $t[11] = 0.49, NS$). These data are also confirmed by the calculated Q_0 values, which measure the number of cocaine infusions rats earn at the hypothetical price of zero. There was no significant difference in Q_0 values between the two groups (independent-samples t -test: $t[11] = 1.88, p = .09$).

The group mean consumption of the reinforcer as well as the exponential model fit (Equation 1) are shown in Figure 2A. Fig. 2B shows the same data in normalized units. The exponential model fit the data well, with an R^2 value of 0.96 for both groups. As can be seen in Figure 2B, rats in the C group worked harder to defend their baseline consumption of cocaine than did the rats in the N group. A comparison of the EV for cocaine between the two groups, based on individual subjects' demand curves, confirmed these findings. Figure 3A shows that the mean EV for cocaine was significantly higher for the C group than for the N group (independent samples t -test: $t[11] = 3.01, p < .01$).

Experiment 2

Nine N-group and nine C-group rats completed the experiment. The other two rats were dropped because they failed to acquire the lever-pressing response within the allocated number of sessions. Only the data from rats that completed the study are included here.

Figure 4A shows the percentage change in body weight from the baseline for each group over four weeks. A 2×2 repeated measures ANOVA indicated that body weight significantly increased over time ($F[4,64] = 34.89, p < .0001$). There was no significant

effect of group on body weight ($F[1,64] = 0.05$, NS). Figure 4B shows the mean amount of liquid consumed by each group over four weeks. A 2×2 repeated measures ANOVA indicated that there was no significant difference between groups in the amount of liquid consumed ($F[1,56] = .06$, NS), and no significant main effect of time ($F[4,56] = 0.84$, NS). Based on body weight and liquid consumption, the nicotine dose (mg/kg/day) was calculated. Figure 4C shows that across the 5 weeks of the experiment, rats consumed an average of 1.21 mg/kg/day ($SD = 0.06$).

Rats required a mean of $8.4 (\pm .97 \text{ SEM})$ sessions to reach the acquisition criterion on the FR-1 schedule. There was no significant difference in the number of sessions required to meet criterion between the N and C groups (independent samples t -test: $t[16] = 0.33$, NS). Averaged over the final three FR-1 sessions, rats obtained a mean of $53.4 (\pm 0.8 \text{ SEM})$ food reinforcers. There was no significant difference in the average number of earned reinforcers over these sessions between the N and C groups (independent samples t -test: $t[16] = 0.97$, NS). These data are also confirmed by the calculated Q_0 values, which reflect the expected number of earned reinforcers at price zero. There was no significant difference between the Q_0 values of the two groups (independent-samples t -test: $t[16] = 0.92$, NS).

The group mean consumption of sucrose pellets as well as the exponential model fit (Equation 1) are shown in Figure 5A. Fig. 5B shows the same data in normalized units. The exponential model fit the data well, with R^2 values of 0.97, and 0.92 for the N and C groups, respectively. As can be seen in Figure 5, the groups did not differ in how hard they worked to maintain their baseline consumption of food. A comparison of the EV for sucrose between the two groups, based on individual subjects' demand curves, confirmed these findings. Figure 3B shows that there is no significant difference in the EV for sucrose between the two groups (independent samples t -test: $t[16] = 0.89$, NS).

Discussion

Experiment 1 presents the first data on how nicotine affects demand for cocaine in rats. In this experiment, we demonstrated that adult male rats preexposed to nicotine in their drinking water did not defend their baseline consumption of cocaine as readily as did control rats. However, there were no other measured significant differences between the two groups.

While the amount of liquid consumed did not differ between the two groups, the rats drank more in their first week than subsequently. It is possible that the sweet taste of the water caused the rats to drink more in the first week until they habituated to it. Previous studies have also shown that rats may drink more saccharin, or water in general, in response to some stressors (Vaswani et al., 1983; Pijlman et al., 2003). It is therefore possible that the stress caused by recent surgery caused an initial increase in response to the sweet-tasting water.

The Q_0 values, which measure the hypothetical consumption of cocaine when price is zero, were not different between the two groups. This means that the C group did not have higher unconstrained, baseline demand for cocaine than the N group, but rather that they worked harder to defend baseline consumption as price increased. There was also no difference between the groups' acquisition of the lever-pressing response for cocaine. It is therefore

unlikely that the results are due to a difference in learning. Taken with the fact that the Q_0 s did not differ, we can conclude that the rats learned to self-administer cocaine at equal rates and had similar baseline demand for cocaine. The differences in self-administration do not become apparent until FR 24 (see Figure 2), indicating that the group difference is derived not from baseline demand, but from the willingness of each group to defend its baseline consumption of cocaine.

One possible explanation for these results lies in each group's general motivation to work for a reward. In such a case, we might find that rats preexposed to nicotine work less hard than the control group for any reward. By this logic, we should see the same effects when this study is repeated with sucrose, instead of cocaine, as the reward. This notion was tested in Experiment 2.

In contrast to the results of Experiment 1, there was no difference between the N and C groups. This suggests that the effect observed in Experiment 1 was specific to cocaine and was not due to a general effect on rats' willingness to work for a reinforcer as its price increases.

We note that it is unlikely the differences between our two experiments were due to the different progression of FR sizes. Experiment 2 used a more rapidly progressing sequence than in Experiment 1 because it was expected that rats would work harder for sucrose pellets than for cocaine. Our goal in choosing ratio sizes was to capture key features of the demand curve, especially the transition from inelastic to elastic demand. Although rats in Experiment 2 did not complete as many ratios as expected, there were enough data points to produce good model fits (R^2 values of 0.97 and 0.92, for the two groups in Experiment 2). Figure 2 shows that in Experiment 1 a clear difference in consumption between the groups emerged when the ratio was increased to FR 24. Rats were trained on FRs 1, 3, 6, and 12 prior to that point. In Experiment 2, there was no difference between the groups in consumption through FR 27 (the ratio closest to FR 24). Prior to that point, rats were trained on FRs 1, 3, and 9. Thus, rats in Experiment 2 had only one fewer ratio than rats in Experiment 1 over the part of the curve where the effect of nicotine pretreatment appeared in Experiment 1.

In Experiment 1, rats in both groups drank about 50 ml of the sweetened fluid during the first week of exposure and consumption subsequently leveled off to about 35 ml per week. In contrast, rats in both groups of Experiment 2 consistently drank approximately 35 ml of fluid throughout the experiment. The only difference in the way that the rats from the two experiments were treated through week 1 was that the subjects in Experiment 1 had surgery a few days before being given access to the fluid. As noted previously, stress can produce an increase in consumption of sweetened fluids. The stress associated with surgery may have accounted for the heightened drinking observed early in Experiment 1.

While this experiment provides some of the first data on the effect of nicotine on cocaine demand in adult male rats, previous studies have assessed the effect of nicotine on food demand. Cassidy and Dallery (2012) investigated the effect of nicotine on demand for food, and also found that nicotine pre-exposure did not alter the elasticity of demand for food.

Therefore, the presence of nicotine may have an impact on the way in which rats value cocaine, but not food.

As noted previously, earlier studies found that nicotine preexposure had mixed effects on cocaine self-administration in male rats. These and the present study all used different nicotine administration regimens. In the present study, rats received nicotine in their drinking water for eight days prior to beginning cocaine self-administration and continued to receive nicotine for the rest of the experiment. Bechtholt and Mark (2002), who found that acute nicotine decreased cocaine taking and chronic nicotine increased cocaine taking, used a regimen of experimenter-administered, single s.c. injections given three min prior to each cocaine self-administration session. The rats did not get any nicotine in the days prior to self-administration training. Horger et al. (1992), who found nicotine pretreatment facilitated the acquisition, but not asymptotic rates, of cocaine self-administration, provided nicotine injections for nine days prior to self-administration of cocaine. However, the rats were not provided any nicotine on the days when they self-administered cocaine. Pomfrey et al. (2015), who found no effect of nicotine pretreatment on cocaine taking, injected rats with nicotine on post-natal day (PND) 28 until PND 43, and tested for cocaine self-administration beginning on PND 81–85. Reed and Izenwasser (2017) used a procedure similar to that of Pomfrey et al. (i.e., rats had a 30-day drug-free period between nicotine preexposure and the beginning of cocaine self-administration), but found that nicotine preexposure increased cocaine self-administration in rats that were preexposed in adolescence, but not adulthood.

In addition to differences in timing of the nicotine administrations relative to cocaine self-administration training, these prior studies all used experimenter-administered injections of nicotine. It is likely that these rats experienced a brief spike in nicotine levels that dissipated fairly quickly each day. When a s.c. injection is used, nicotine can reach peak brain levels within 15 min (Matta et al., 2007) but is rapidly cleared, with an estimated half-life in the rat of about an hour (Kyrematen et al., 1998; Ghosheh et al., 1999). Thus, in studies like that of Bechtholt and Mark (2002), rats would have spent most of their day not experiencing the effects of nicotine. In studies like those of Pomfrey et al. (2015) and Reed and Izenwasser (2017), rats were at least 30 days removed from their last experience of nicotine at the time they began self-administration training. In contrast, our N group had unlimited access to a nicotine solution (except when in the operant chamber) every day during the cocaine self-administration phase (and for eight days prior to beginning self-administration). While we did not measure hourly fluid intake, Kita et al. (1985) found that rats drank nicotine-laced water at a fairly consistent rate during the period when they were awake. Assuming our rats did so also, they would have had nicotine in their blood and brain for longer time periods each day than rats in studies where only a single daily experimenter-administered injection of nicotine was given.

The oral nicotine pretreatment regimen used in the present study was most similar to that used by Levine et al. (2011) in mice. They found that nicotine enhanced cocaine-induced CPP. As noted previously, the CPP paradigm tests the conditioned Pavlovian effects of drugs, but not necessarily the reinforcing effects of the drug needed to maintain operant behavior (Bardo and Bevins, 2000). While drugs that induce CPP effects are usually readily self-administered by rats, the two measures are not always correlated. Deroche et al. (1999)

measured cocaine self-administration in rats with 6-week, or 29-week access, and also assessed both groups for cocaine CPP. While the rats with 29-week access self-administered more cocaine than the 6-week group, there was no difference in CPP between the groups. Thus, while CPP might demonstrate the rewarding effects of a drug, it does not necessarily demonstrate the amount of drug that a rat will consume or rats' willingness to defend that consumption. Furthermore, there is evidence that different neural systems are involved in these two paradigms. D₂ dopamine receptor antagonists act to reduce cocaine self-administration, but have no effect on cocaine CPP (see Bardo and Bevins, 2000). It is therefore difficult to compare the present results with data on the effect of nicotine on cocaine CPP, as the two paradigms might capture separate effects of nicotine on cocaine consumption.

On average, our rats drank 1.31 mg/kg/day of nicotine in Experiment 1 and 1.21 mg/kg/day in Experiment 2. While we did not assess the plasma levels of nicotine or its metabolite cotinine in our rats, previous studies using similar doses of nicotine in rats' drinking water found that such doses can produce plasma concentrations of nicotine or cotinine approximating those found in human smokers. For example, Welzl et al. (1988) dissolved nicotine in rats' drinking water at a concentration of 20 mg/l – close to the 15 mg/l concentration used here – and found plasma nicotine levels of 16.6 ng/ml. This falls within the range (15–40 ng/ml) of nicotine plasma concentrations found in human smokers (Feyerabend et al., 1985; Russell et al., 1986; Shoaib and Stolerman, 1999). Similarly, Bordia et al. (2008) and Perez et al. (2015) put nicotine in rats' drinking water at a concentration of 25 mg/L and found cotinine plasma levels of 275–300 ng/ml, which is close to the plasma cotinine concentration found in smokers of ~30 cigarettes per day (Benowitz et al., 1983; Russell et al., 1986). Because our concentration of nicotine in drinking water was somewhat lower than that used by Bordia et al. (2008) and Perez et al. (2015), it might be expected that cotinine levels in our rats were closer to those found in moderate smokers rather than 30 cigarettes/day smokers. However, it should be noted that rats adjust their drinking of nicotine water such that they drink less of solutions with higher nicotine concentrations than they do of solutions with lower concentrations (Kita et al., 1985). Thus, although a lower concentration of nicotine in the drinking water was used here than in the studies by Bordia et al. (2008) and Perez et al. (2015) (who did not report how much fluid rats drank), it is possible that rats in our study achieved nicotine and cotinine plasma levels similar to those of rats in their studies by drinking more solution.

A limitation of the present study is that only male rats were used. All of the previous studies investigating the effects of nicotine preexposure on cocaine self-administration described above (Bechtholt and Mark, 2002; Horger et al., 1992; Pomfrey et al., 2015; Reed and Izenwasser, 2017) also only used male rats. Future studies will be needed to determine whether nicotine preexposure affects cocaine-taking behavior similarly in females and males. While there is evidence from different procedures that females may be more sensitive to the reinforcing effects of cocaine (for review, see Lynch, 2017), sex differences in response to nicotine seem to be more variable. Previous studies (not involving cocaine self-administration) have found that nicotine can sometimes produce an effect on behavior in males but not females (e.g., Collins et al., 2004; Klein et al., 2001) or in females but not males (e.g., Trauth et al., 2000), can produce opposite effects in females and males (Quick et

al., 2014), or produce stronger effects in one sex than in the other (Harrod et al., 2004). It is therefore important to note that results reported here with male rats may not generalize to female rats. There is clearly much work that needs to be done in investigating potential sex differences in the effects of nicotine preexposure on cocaine self-administration.

Another limitation of the present study is the use of a single 0.7 mg/kg/infusion cocaine dose. It is possible nicotine could have had a different effect on elasticity of demand for cocaine if a different cocaine dose had been used. A strength of the exponential demand model, however, is that it inherently controls for reinforcer magnitude (or “package size”) effects (Hursh and Silberberg, 2008). It has been shown previously that the elasticity of rats’ demand for cocaine was independent of dose when using doses above a minimum threshold. Kearns and Silberberg (2016) tested elasticity of demand for three doses of cocaine (0.11, 0.33, and 1.0 mg/kg/infusion), and found that demand elasticity was equivalent for the two higher doses, but demand was more elastic for the lower dose (which was near the lowest dose that is still reinforcing in rats). A similar result has also been found in monkeys responding for cocaine (Winger 1993; Winger et al., 2006). The dose used in the current study was intermediate to the two doses that Kearns and Silberberg found did not differ in terms of demand elasticity. Thus, we would not expect rats’ elasticity of demand for cocaine to change if different (above threshold) cocaine doses had been used here, at least in the control rats. A question for future studies is whether nicotine pre-treatment interacts with cocaine dose such that the effect of nicotine on the elasticity of demand for cocaine depends on the cocaine dose.

Consideration of previous studies investigating the effects of nicotine on cocaine self-administration might yield information about the role of cocaine dose. The two previous studies most closely related to the present one also used only one cocaine dose. Bechtholt and Mark (2002) examined acute nicotine exposure prior to cocaine self-administration sessions using a only a 0.25 mg/infusion cocaine dose; this dose is similar to the one used in the present experiment (0.7 mg/kg/infusion). They found that a high dose of nicotine acutely decreased responding on a PR schedule for this dose of cocaine, whereas chronic nicotine pre-treatment increased PR schedule responding for cocaine. As noted previously, however, PR schedule responding does not necessarily reflect elasticity of demand (Lamb and Daws, 2013). Horger et al. (1992) used only a 0.25 mg/kg/infusion dose of cocaine and found that nicotine pre-exposure (which was discontinued during the cocaine self-administration phase) facilitated the acquisition of cocaine self-administration, but had no effect on asymptotic levels of cocaine taking. This is consistent with the finding in the present experiment that nicotine had no effect on baseline (Q_0) levels of cocaine taking. The studies of Pomfrey et al. (2015) and Reed and Izenwasser (2017) are more difficult to compare to the present study because they used a brief nicotine preexposure period followed by a 30- to 42-day drug-free period prior to beginning cocaine self-administration training. Pomfrey et al. (2015) used 0.25 and 0.75 mg/kg/infusion doses of cocaine and found no effect of adolescent nicotine pre-exposure on FR-1 or PR schedule responding for cocaine in adulthood. Reed and Izenwasser (2017), on the other hand, found that nicotine pre-exposure in adolescence increased FR-1 schedule responding for cocaine in adulthood across cocaine doses ranging from 0.06 to 1.0 mg/kg/infusion, with no significant interaction of pretreatment (nicotine vs. vehicle) with cocaine dose. Adult preexposure to nicotine had no effect on responding for

cocaine across the same range of doses. Though difficult to compare that study to the present one, this limited amount of data suggests that when nicotine preexposure has an effect on cocaine self-administration, it is not cocaine dose-dependent.

It does not appear that the effect of nicotine in the present study was due to a shifting of the cocaine dose-response curve to the left or right. If there were a leftward shift, it would be expected that nicotine preexposed rats would self-administer fewer 0.7 mg/kg cocaine infusions of cocaine at FR 1, since this dose is on the descending limb of the dose-response curve. Instead, there was no difference between nicotine and control rats in baseline consumption of cocaine. Previous studies exploring the relationship between changes in dose-response curves and changes in demand indicate that decreased demand elasticity is associated with an upward, and not leftward or rightward, shift in the dose-response curve. For example, extended access to cocaine causes demand for cocaine to become less elastic and also causes an upward shift of the dose-response curve (Ahmed and Koob, 1998; Christensen et al., 2008b). The finding in the present experiment that nicotine pre-exposure increased the elasticity of demand for cocaine would suggest a downward shift of the dose-response curve, if any change.

The baseline rate of responding was much higher for sucrose (53 reinforcers per session on FR 1) in Experiment 2 than for cocaine (17 reinforcers per session on FR 1) in Experiment 1. Potential rate-dependent effects of nicotine therefore should be considered when comparing the outcomes of the two experiments. Nicotine, like other drugs, can produce an increase in the frequency of low rate behaviors and a decrease in the frequency of high rate behaviors (Goldberg et al., 1989; Perkins, 1999). If FR 1 cocaine self-administration were a low rate behavior, it might have been expected that nicotine would increase rates of cocaine self-administration. However, we did not find any effect of nicotine on baseline cocaine taking, but instead found that nicotine actually decreased rats' willingness to work for cocaine as its price increased. In Experiment 2, rats responded at a relatively high rate for sucrose (compared to responding for cocaine). It might be expected that nicotine would decrease high baseline rates of responding. But there was no effect of nicotine on baseline sucrose taking or on the elasticity of demand for sucrose. Thus, it does not appear that simple rate-increasing or rate-decreasing effects of nicotine could account for the pattern of results from Experiments 1 and 2.

An additional difference between Experiments 1 and 2 is that rats were tethered during cocaine self-administration sessions in Experiment 1, but they were not tethered in Experiment 2 (since they were only responding for sucrose pellets). However, it is important to note that in both experiments, both the nicotine and control groups were treated the same with respect to tethering. Thus, the tethering variable was held constant across levels of the pretreatment independent variable (nicotine vs. control) in each experiment. It is theoretically possible that tethering could have interacted with the pretreatment independent variable to produce an effect in Experiment 1 but not Experiment 2, but the mechanism through such an interaction might occur is not clear. In a previous experiment from our lab (Schwartz et al., 2017), using procedures similar to those used here, rats that were tethered earned (on an FR-1 schedule) an average of 50 liquid saccharin reinforcers per session, which is comparable to the 53 sucrose pellets earned per session by the rats in Experiment 2

here. While it is hard to compare responding for these different types of reinforcers, this data at least indicate that tethered rats are capable of responding at the relatively high rates observed in Experiment 2.

Our results present the first evidence of the effect of nicotine on demand for cocaine in adult male rats. We found that nicotine preexposure increases the elasticity of demand for cocaine, but not of food, in adult male rats. Our data complement studies that have found that nicotine attenuates positive subjective responses to cocaine in humans (Kouri et al., 2001), and decreases rats' cocaine consumption in some cases (Bechtholt and Mark, 2002). However, as mentioned, these effects may be dependent on the specific parameters of the nicotine pretreatment regimen. Further study is required to assess how different nicotine pretreatment regimens may interact with cocaine in self-administration studies. Future studies are also needed to determine how females might differ from males in how nicotine preexposure affects demand for cocaine.

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Figure 1.

(A) Group mean ($\pm$ SEM) percent change in body weight over the duration of Experiment 1.

(B) Group mean ($\pm$ SEM) ml of liquid consumed over the duration of Experiment 1. **(C)**

Nicotine group mean ($\pm$ SEM) dose of nicotine over the duration of Experiment 1.

Figure 2.

(A) Group mean demand for cocaine in the nicotine and control groups in Experiment 1: numbers of cocaine infusions earned at each FR plus demand curves fit by Equation 1. (B) Normalized consumption as a function of normalized price as well normalized demand curves fit by Equation 1. Consumption is normalized by expressing the numbers of reinforcers earned as a percentage of Q_0 . Normalized price is the number of responses required at a particular FR to obtain 1% of Q_0 .

Figure 3. (A) Mean (+ SEM) essential value of cocaine for the N and C groups. (B) Mean (+ SEM) essential value of food for the N and C groups.

Figure 4.

(A) Group mean ($\pm$ SEM) percent change in body weight over the duration of Experiment 2.

(B) Group mean ($\pm$ SEM) ml of liquid consumed over the duration of Experiment 2. (C)

Nicotine group mean ($\pm$ SEM) dose of nicotine over the duration of Experiment 2.

Figure 5.

(A) Group mean (+ SEM) demand for food in the nicotine and control groups in Experiment 2: numbers of food reinforcers earned at each FR plus demand curves fit by Equation 1. (B) Normalized consumption as a function of normalized price as well normalized demand curves fit by Equation 1. Consumption is normalized by expressing the numbers of reinforcers earned as a percentage of Q_0 . Normalized price is the number of responses required at a particular FR to obtain 1% of Q_0 .