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Heroin and saccharin demand and preference in rats*

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Abstract

Background—Several recent studies have investigated the choice between heroin and a non-drug alternative reinforcer in rats. A common finding in these studies is that there are large individual differences in preference, with some rats preferring heroin and some preferring the non-drug alternative. The primary goal of the present study was to determine whether individual differences in how heroin or saccharin is valued, based on demand analysis, predicts choice.

Methods—Rats lever-pressed for heroin infusions and saccharin reinforcers on fixed-ratio schedules. The essential value of each reinforcer was obtained from resulting demand curves. Rats were then trained on a mutually exclusive choice procedure where pressing one lever resulted in heroin and pressing another resulted in saccharin. After seven sessions of increased access to heroin or saccharin, rats were reexposed to the demand and choice procedures.

Results—Demand for heroin was more elastic than demand for saccharin (i.e., heroin had lower essential value than saccharin). When allowed to choose, most rats preferred saccharin. The essential value of heroin, but not saccharin, predicted preference. The essential value of both heroin and saccharin increased following a week of increased access to heroin, but similar saccharin exposure had no effect on essential value. Preference was unchanged after increased access to either reinforcer.

Conclusion—Heroin-preferring rats differed from saccharin-preferring rats in how they valued heroin, but not saccharin. To the extent that choice models addiction-related behavior, these results suggest that overvaluation of opioids specifically, rather than undervaluation of non-drug alternatives, could identify susceptible individuals.

Keywords

heroin self-administration; demand; essential value; choice; saccharin; rats

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Contributors

All authors contributed to the design of the experiment. Lindsay Schwartz and David Kearns performed the experiment. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

1. Introduction

Recently, a number of studies have investigated choice between heroin and non-drug reinforcers in rats (Lenoir et al., 2013; Madsen and Ahmed, 2015; Tunstall et al., 2014; Vandaele et al., 2015). This interest has been stimulated by the observation that preference for drugs over non-drug alternatives may model aspects of addiction (Ahmed, 2010). A common finding in studies with rats is that there are large individual differences in preference, with some rats consistently choosing heroin while others prefer the non-drug alternative.

The factors responsible for these individual differences are not well understood. The present study was designed to investigate whether differences in the ways that rats value heroin or a non-drug alternative (saccharin, in this case) account for the choices they make. In a mutually exclusive choice situation, heroin preference could result from either high heroin valuation or low saccharin valuation. That is, heroin-preferring rats could differ from saccharin-preferring rats in terms of how they value heroin, with there being no difference in how these subsets of rats value saccharin. Alternatively, heroin- and saccharin-preferring rats may value heroin comparably, but saccharin-preferring rats may value saccharin more highly than do heroin-preferring rats. Either of these possibilities, or a combination of the two, would be expected to lead to heroin preference.

Essential value (EV), a behavioral economic measure that covaries with inelasticity of demand (Hursh and Silberberg, 2008), was used to index reinforcer value. EV quantifies how hard subjects work to defend baseline consumption levels of a reinforcer as the price of that reinforcer increases. EV is especially useful in a study such as the present one because EV is independent of reinforcer magnitude (Hursh and Silberberg, 2008), thus facilitating comparisons of different reinforcers. A growing number of recent studies investigating drugs as reinforcers have used EV to quantify reinforcer value (e.g., Bentzley et al., 2013, 2014; Grebenstein et al., 2015; Hofford et al., 2016; Huskinson et al., 2016; Lamb and Daws, 2013; Lemley et al., 2016).

The primary goal of the present study was to investigate how the EVs of heroin and saccharin relate to the choice between these reinforcers. The design of this study also allowed for a comparison of the EVs of heroin and a non-drug reinforcer in rats. This information adds to the results of research comparing the EVs of other drugs and non-drug alternatives in rats. Previous studies found that, when directly compared, food (in hungry rats) had higher EV than cocaine (Christensen et al., 2008a, 2009; Kearns et al., 2016) or methamphetamine (Galuska et al., 2011), whereas saccharin (in non-fluid-deprived rats) and cocaine had similar EVs (Kearns et al., 2016). The present study extends this research, which has focused on psychostimulants thus far, to another drug class by using the opioid heroin as the drug reinforcer.

An additional goal of the present study was to investigate how increased access to heroin or saccharin alters demand for these reinforcers and the choice between them. In an earlier study, Christensen et al. (2008b) found that just seven additional two-h cocaine self-administration sessions made demand for cocaine less elastic (i.e., the EV of cocaine

increased). In contrast, similar exposure to a schedule of food reinforcement did not alter the elasticity of demand for food. The present study used a design similar to that of Christensen et al. (2008b) to determine whether the elasticity of demand for heroin or saccharin, as well as preference between them, changes as a result of increased access to these reinforcers.

2. Materials and Methods

2.1. Subjects

Twenty naïve adult male Long-Evans rats, weighing approximately 450 g at the start of the experiment, served as subjects. Rats were individually housed in plastic cages with wood-chip bedding and had unlimited access to rat chow and water in their home cages. The colony room where the rats were housed had a 12-h light:dark cycle with lights on at 08:00 h. Training sessions were conducted five days per week during the light phase of the light:dark cycle. Throughout the experiment, 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.

2.2. Apparatus

Training took place in 10 standard operant test chambers described in detail elsewhere (Tunstall and Kearns, 2014). The essential features of each chamber were two retractable levers, a retractable sipper tube and bottle, cue lights above each lever, and a speaker used to provide a tone (4000 Hz and 70 dB) stimulus. Heroin (provided by the Drug Supply Program, National Institute on Drug Abuse, Bethesda, MD) in a saline solution at a concentration of 0.0512 mg/ml was infused at a rate of 3.19 ml/minute by 10-ml syringes driven by Med-Associates (St. Albans, VT) syringe pumps. Tygon tubing extended from the 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. Heroin was delivered to the subject through Tygon tubing that passed through the metal spring of the tether apparatus.

2.3. Surgery

Before training, 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). In brief, approximately 3.5 cm of Silastic tubing was inserted into the right jugular vein. From this insertion site, an additional 8 cm of Silastic tubing passed under the skin to the midscapular region where it connected to the 22-gauge stainless steel tubing of a backmount catheter port (Plastics One, Roanoke, VA) that was implanted subcutaneously. The spring tether in the chamber was attached to the threaded plastic cylindrical shaft of the port that protruded through an opening in the skin. All surgery was conducted under ketamine (60 mg/kg) and xylazine (10 mg/kg) anesthesia. Rats were given 7–10 days to recover from surgery. Catheters were flushed daily with 0.1 ml of a saline solution containing 1.25 µg/ml heparin and 0.08 mg/ml gentamicin.

2.4. Procedure

See Fig. 1 for a schematic diagram showing an overview of the procedure.

2.4.1. Phase 1: Demand for Heroin and Saccharin—The demand procedure used here was similar to that in Christensen et al. (2008a). Rats were first trained to lever press for heroin and for saccharin on a fixed-ratio (FR)-1 schedule. During sessions lasting 3 h, there were eight 15-min components where one of the two retractable levers was inserted. There were four presentations each of the heroin and saccharin levers, with the order of presentation randomized with the restriction that there were no more than two consecutive components of the same type. Each component was followed by a 7.5-min period where both levers were retracted. Thus, over the course of the 3-h session, rats had access to each of the levers for a total of 60 min. The position (left vs. right) of the heroin and saccharin levers was counterbalanced over rats. During heroin-lever components, a lever press resulted in a 0.02-mg/kg heroin infusion, simultaneous illumination of the cue light above the lever, and a 10-s tone presentation. During saccharin-lever components, pressing the lever resulted in the saccharin sipper tube being inserted into the chamber for 20 s, allowing rats to drink the 0.2% (w/v) saccharin solution. The 0.02-mg/kg/infusion dose was used because previous studies have found that this dose supports maximal responding in rats (Martin et al., 1998). Our goal was to try to make the baseline numbers of heroin and saccharin reinforcers obtained as comparable as possible because a previous study (Kearns et al., 2016) found that essential value is most useful as a predictor of preference between reinforcers when they maintain similar baseline consumption levels.

Rats were trained on this procedure with an FR-1 schedule for a minimum of eight sessions and until the consumption of each reinforcer stabilized. Stability was defined as three consecutive sessions where the total number of reinforcers earned of each type did not vary from the rolling three-session mean by more than 20%. Once this stability criterion was reached, the FR increased over blocks of two sessions according the following sequence: 3, 10, 32, 100, 320. The progression of the sequence ended early if a rat's consumption of both reinforcers at a particular FR declined to less than 10% of consumption observed at FR 1.

2.4.2. Phase 2: Choice between Heroin and Saccharin—Upon completion of demand testing, rats were trained on a discrete-trials choice procedure like that introduced by Cantin et al. (2010) and used by Tunstall and Kearns (2013, 2014, 2015). Each session began with four forced-choice trials. There were two forced-choice trials each with the heroin and saccharin levers, with trial order randomized within blocks of two. These forced-choice trials ensured that rats sampled each lever twice at the beginning of each session. On a heroin trial, the heroin lever was inserted into the chamber and a single lever press resulted in delivery of a heroin infusion (0.02 mg/kg/infusion), presentation of the associated 10-s audiovisual cue, and retraction of the lever. On a saccharin trial, the saccharin lever was inserted and a single lever press resulted in access to the saccharin sipper tube and retraction of the lever. Each trial was followed by a 10-min intertrial interval (ITI). Following the four forced-choice trials, there were 14 free-choice trials. Now, both levers were inserted simultaneously. A single press on the selected lever resulted in delivery of the designated reinforcer and retraction of both levers. (That is, an FR-1 schedule was in effect on both

levers.) A 10-min ITI followed each free-choice trial. Rats were trained on this procedure for at least five sessions and until preference stabilized. The stability criterion was three consecutive sessions on which the percentage of choices for heroin did not differ from the rolling three-session mean by more than 20 percentage points.

Once this criterion was reached, rats were tested over an additional five sessions on a choice procedure where the FR in effect on the saccharin lever increased according to the sequence 2, 4, 8, 16, 32. Heroin was always available on an FR-1 schedule. All other aspects of the choice procedure were the same as described above. The goal of this procedure was to obtain an additional measure of the strength of preference in case a restricted range of the primary preference measure (percent choice when both reinforcers were available on an FR-1 schedule) obscured correlations between preference and EV. Restriction of range was ultimately not a problem.

2.4.3. Phase 3: Increased Access to Heroin or Saccharin—Upon completion of demand and choice testing, half the rats received increased heroin access (the Heroin group) and the other half received increased saccharin access (the Saccharin group). Group assignment was made with the goal of matching the groups as closely as possible on heroin EV, saccharin EV, and preference. Both groups completed seven 3-h sessions, where only the heroin lever or the saccharin lever was inserted into the chamber for the entire session and presses on that lever were reinforced on an FR-1 schedule.

2.4.4 Phase 4: Redetermination of Demand for Heroin and Saccharin—After the completion of the increased-access sessions, rats were trained on the same demand procedure used in Phase 1 to redetermine the EVs of heroin and saccharin.

2.4.5. Phase 5: Redetermination of Preference—Rats were trained on the same choice procedure used in Phase 2 to determine whether increased access to heroin or saccharin affected preference.

2.5. Data Analysis

For the demand data, the number of heroin infusions self-administered and the number of saccharin reinforcers earned were averaged over the training sessions at each FR (for FR 1, the mean of the three criterion sessions was used). Individual and group mean consumption data were fit by Hursh and Silberberg's (2008) exponential-demand equation:

$$\log Q = \log Q_0 + k(e^{-aQ_0^C} - 1), \quad (1)$$

where Q is quantity consumed, Q_0 is consumption as price approaches 0, k is a constant defining the consumption range in log units ($k = 3.5$ here), a determines the rate of decline in consumption, and C is cost (FR size). Demand curves are presented in two ways. First, the number of reinforcers earned was plotted as a function of FR size. Then, to facilitate comparison of demand elasticity across reinforcers when baseline consumption differed, normalized consumption was plotted as a function of normalized price (Christensen et al., 2008a). To normalize consumption, the number of heroin infusions and saccharin reinforcers

obtained was expressed as percentage of Q_0 , the consumption level predicted by the model as price approaches 0. Price was normalized by converting it to the number of responses required at a particular FR to obtain 1% of Q_0 .

The primary measure of interest from the demand phases was EV. This was based on the model fits to the individual subjects' consumption data and was calculated according to the formula given by Hursh (2014):

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

T-tests and/or ANOVAs were used to compare the EV of heroin and saccharin and to evaluate changes in EV after the increased-access phase.

For the choice data, the percentage of free-choice trials on which heroin was chosen, averaged over the three criterion FR-1 sessions, was the primary measure of preference. A rat was classed a heroin preferer if it chose heroin on greater than 50% of trials whereas it was classed a saccharin preferer if it chose heroin on less than 50% of trials. One-sample *t*-tests were used to compare mean preference to 50%, the score expected if rats were indifferent between heroin and saccharin. Pearson correlation coefficients were used to measure the strength of association between preference and the EVs of heroin and saccharin. ANOVAs and *t*-tests were used to evaluate consumption during the increased access phase and to evaluate possible changes in EV and preference after the increased-access phase.

For all statistical tests, α was set to 0.05. The Benjamini-Hochberg (1995) procedure was used to control the false discovery rate at 0.05 for collections of multiple related *t*-tests.

3. Results

3.1. Phase 1: Demand for Heroin and Saccharin

Rats required a mean of 20.2 ($\pm$ 2.0 SEM) sessions to reach the acquisition criterion on the FR-1 schedule. Averaged over the final three FR-1 sessions, rats obtained a mean of 14.1 ($\pm$ 2.1 SEM) heroin infusions and 49.5 ($\pm$ 5.6 SEM) saccharin reinforcers. Fig. 2a shows group mean consumption of each reinforcer as well as the exponential model fit. Only data from FR 1, 3, 10, and 32 are presented because these were the FRs on which all subjects were tested. (If consumption was already below 10% of baseline at FR 32, a rat was not tested at higher ratios.) Fig. 2b shows the same data in normalized units. The exponential model fit the group mean data well, with R^2 values of 0.98 and 0.99 for heroin and saccharin, respectively. The mean R^2 based on fits to individual subjects' data were 0.93 and 0.97 for heroin and saccharin, respectively. As can be seen in Fig. 2b, rats worked harder as price increased to defend consumption of saccharin than they did to defend consumption of heroin. A comparison of the EVs for heroin and saccharin based on individual subjects' demand curves (which included consumption data at all FRs on which the rat was tested) confirmed these findings. Figure 2c shows that the mean EV for saccharin was significantly higher than that for heroin (paired-samples *t*-test: $t[19] = 3.5$, $p < 0.005$).

3.2. Choice between Heroin and Saccharin

Rats required a mean of $6.1 (\pm 0.4 \text{ SEM})$ sessions to meet the stability criterion on the choice procedure. Fig. 3a presents percent choice of heroin averaged over the three criterion sessions for individual subjects. Rats chose heroin on a mean $28.6\% (\pm 5.7\% \text{ SEM})$ of trials. This mean was significantly lower than 50% (indifference; one-sample t -test: $t[19] = -3.8, p < 0.005$).

Fig. 3b shows the results from the five additional choice sessions where the FR on the saccharin lever was increased over sessions. Mean percent choice of heroin remained significantly below 50% from FR 2 through FR 8 ($t[19]s = 2.4, ps < 0.03$) and only increased significantly above 50% when the FR for saccharin was increased to 32 ($t[19] = 2.7, p = 0.015$).

Fig. 3c shows that there was a significant positive association between the EV of heroin and percent choice of heroin (Pearson $r = 0.63, p < 0.005$). In contrast, there was no association between the EV of saccharin and preference (Fig. 2d; Pearson $r = 0.12, p > 0.60$).

Fig. 4 presents the mean ($\pm \text{SEM}$) EVs of heroin and saccharin for heroin preferers ($n = 3$) and saccharin preferers ($n = 15$). Two rats chose heroin or saccharin on exactly 50% of trials and so were not classed as preferers of either reinforcer. The EV of heroin was over three times larger in heroin preferers than it was in saccharin preferers. In contrast, the EV of saccharin was comparable across groups. Because of the large difference in variance across groups, non-parametric statistics were used here to compare groups. Robust rank-order tests (Siegel and Castellon, 1988; Feltovich, 2005) indicated that the EV of heroin differed over groups ($U[3,15] = 3.6, p < 0.025$), but the EV of saccharin did not ($U[3,15] = -0.3, p > 0.1$).

3.3. Increased Access to Heroin or Saccharin

Supplemental Fig. S1¹ shows mean ($\pm \text{SEM}$) consumption of heroin or saccharin reinforcers during the seven increased-access sessions for the Heroin group ($n = 9$) and the Saccharin group ($n = 10$). One rat in the Heroin group was lost due to illness. The Saccharin group earned approximately 50–60 reinforcers per session and the Heroin group self-administered approximately 25–30 infusions per session. There was no change in consumption over sessions for either group. A 2×7 (Group $\times$ Session) repeated-measures ANOVA indicated that there was a significant effect of Group ($F[1,17] = 5.1, p < 0.05$), but there was no effect of Session ($F[6,102] = 1.8, p > 0.1$) or Group $\times$ Session interaction ($F[6,102] = 1.2, p > 0.3$). Supplemental Fig. S2¹ shows mean ($\pm \text{SEM}$) bodyweights for each group during the increased-access phase and for each of two weeks before and after this phase. A 2×5 (Week by Group) ANOVA indicated that bodyweights increased over weeks ($F[4,68] = 12.5, p < 0.001$), but there was no effect of Group ($F < 1$) and no Group $\times$ Week interaction ($F[4,68] = 1.6, p > 0.15$).

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3.4. Redetermination of Demand for Heroin and Saccharin

Supplemental Fig. S3¹ shows group mean demand curves for heroin and saccharin as determined before and after the increased-access sessions for the two groups. The exponential demand model accommodated the group mean data well, with R^2 values ranging from 0.96 to 0.99. To evaluate changes in demand elasticity in terms of inferential statistics, EVs for heroin and saccharin based on individual subjects' demand curves were compared. Fig. 5 shows the mean ($\pm$ SEM) EVs of the two reinforcers as determined before and after the increased-access phase for both groups. For the Heroin group, the EVs of both heroin and saccharin were higher after the increased-access phase as compared to before. However, for the Saccharin group, the EVs of both heroin and saccharin were virtually unchanged. A $2 \times 2 \times 2$ [Group $\times$ Time (Before vs. After) $\times$ Reinforcer] mixed ANOVA confirmed these impressions. There was a significant main effect of Reinforcer ($F[1,17] = 7.8, p < 0.05$), a significant main effect of Time ($F[1,17] = 9.9, p < 0.01$), and a significant Time $\times$ Group interaction ($F[1,17] = 4.9, p < 0.05$). All other main effects and interactions were not significant (all F s < 1.2 , all p s > 0.25). Subsequent paired-samples t -tests confirmed that in the Heroin group there was a significant increase in the EV of both heroin ($t[8] = 2.7, p = 0.025$) and saccharin ($t[8] = 4.0, p < 0.005$) after increased access to heroin. There was no change for either reinforcer in the Saccharin group (both $t[9]$ s < 1 , both p s > 0.5).

3.5. Redetermination of Preference

One rat in each group failed to complete the final phase due to illness, reducing the number of subjects to 9 and 8 for the Saccharin and Heroin groups, respectively. Supplemental Fig. S4² shows that both groups chose heroin on approximately 25–30% of trials both before and after the increased access phase. A 2×2 (Group $\times$ Time) mixed ANOVA confirmed that there was no significant effect of Group ($F < 1$), Time ($F < 1$), or their interaction ($F[1,15] = 2.3, p > 0.15$).

4. Discussion

The main finding of the present experiment was that the EV of heroin predicted preference for heroin over saccharin, whereas the EV of saccharin was unrelated to preference. Heroin-preferring rats valued heroin significantly more highly than did saccharin-preferring rats, but these subsets of rats did not differ in how they valued saccharin. In a previous study (Kearns et al., 2016), the EV of cocaine was a positive predictor of cocaine preference, whereas the EV of food or saccharin was a negative predictor of preference. This earlier study used the same demand and choice procedures as those used here. To the extent that choice models addiction-related behavior (Ahmed, 2010), these results suggest that overvaluation of the drug may predispose towards disordered use of heroin or cocaine, whereas undervaluation of non-drug alternatives may be a less important factor in opioid addiction.

The finding that only a small minority of rats preferred heroin under the conditions used in the present experiment is consistent with the results of several recent studies investigating rats' choice between heroin and non-drug alternatives including food (Tunstall et al., 2014)

²Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

or saccharin (Lenoir et al., 2013; Madsen and Ahmed, 2015; Vandaele et al., 2015) under similar conditions. Only when Lenoir et al. (2013) gave rats several weeks of extended access to heroin (self-administration sessions lasting 6 or 9 h), resulting in suppressed body growth and suppression of saccharin drinking (even when it was the only reinforcer available), did group-mean saccharin preference diminish to indifference. That is, even heroin exposure sufficient to produce signs of physical dependence still did not produce mean preference of heroin over saccharin.

Increased access to heroin in the current study resulted in a significant increase in the EV of heroin. Lenoir and Ahmed (2008), using a more intensive extended-access regimen (several weeks of 6-h self-administration sessions), also found that heroin demand became more inelastic with increased heroin exposure. The increased EV of heroin observed in the present study is also consistent with the results of Christensen et al. (2008b), who used a procedure similar to that used here and found that increased access to cocaine increased its EV. In contrast to the effects of increased heroin access, increased saccharin access in the present study did not alter the elasticity of demand for saccharin (or for heroin). This indicates that the outcome observed in the Heroin group was not due simply to the passage of time or to a practice effect, but instead was specifically due to the increased experience with heroin self-administration. The amount of exposure to heroin that the Heroin group received was substantially less than that in previous extended-access studies (Lenoir and Ahmed, 2008; Lenoir et al., 2013). It is possible that an even greater increase in heroin essential value than that observed here would have occurred if greater heroin access were given.

Increased access to heroin also resulted in an increase in the EV of saccharin. As noted by Lenoir et al. (2013), there are commonalities between opioids and sweet rewards observed at the behavioral and neurobiological levels (Colantuoni et al., 2002; Jain et al., 2004; Pecina and Berridge, 1994; Smith and Berridge, 2007). It may therefore be expected that a manipulation that affects the EV of heroin would affect the EV of saccharin similarly. However, in Lenoir et al.'s study, extended access to heroin suppressed baseline consumption of saccharin drinking (demand elasticity was not measured). As noted by Lenoir et al., this was likely due to the effects of heroin withdrawal. Indeed, when tested in withdrawal after 9-h extended-access sessions, even responding for heroin was suppressed. Rats in the present experiment never showed overt signs of heroin withdrawal. Furthermore, during demand testing, heroin components alternated with saccharin components, making it more likely that rats experienced mild acute effects of heroin, rather than withdrawal, during the time when they were working for saccharin. It may be that chronic exposure to heroin increases the value of sweet rewards, but only when those sweet rewards are not experienced in a state of withdrawal. This notion is consistent with the finding that opiate-dependent individuals maintained on methadone or buprenorphine, as well as recently detoxified former addicts (not opioid maintained and not experiencing withdrawal), rate sweet tastes as significantly more pleasant and more intense than do healthy controls (Green et al., 2013).

The present study is one of several recent ones investigating factors related to individual differences in preference for drugs over non-drug alternatives. Previous research with cocaine as the drug reinforcer has identified five variables that predict increased cocaine choice: being a sign-tracker (rather than a goal-tracker; Tunstall and Kearns, 2015), having a

small locomotor response to novelty (Vanhille et al., 2015), having relatively inelastic demand for cocaine (Kearns et al., 2016), having relatively elastic demand for non-drug alternatives (Kearns et al., 2016), and being female (Kersetter et al., 2012). Less is known about the factors that predict preference for opioids. The present study identified high heroin valuation as one predictor of preference. Future research with the model used here could provide additional insight into characteristics that predispose some individuals to consistently choose opioids over non-drug alternatives.

Instead of delivering a fixed amount of saccharin each time a saccharin reinforcer was earned, rats were given 20 s of access to a bottle containing saccharin. This method of presenting the saccharin reinforcer was used to match that of similar previous studies (e.g., Kearns et al., 2016; Lenoir et al., 2013; Madsen and Ahmed, 2014; Vandaele et al., 2015). This method is analogous to that commonly used in operant studies in pigeons, where the food reinforcer is a fixed period of access to a raised magazine filled with food. A possible limitation of the method used here is that the amount of saccharin drunk during presentation of the saccharin reinforcer was under the rats' control. This meant that the unit price of saccharin could be determined in part by the subject and could have varied across saccharin presentations. (With the apparatus used here, it was not possible to measure how much saccharin was drunk on each presentation.) Conceptualizing the alternative reinforcer as the opportunity to drink saccharin may help resolve this interpretational issue. The unit price of the opportunity to drink saccharin was not under the subjects' control, but was determined only by the schedule in effect.

A limitation of the current study is that a single heroin dose and a single saccharin reinforcer magnitude were used. An assumption of the exponential model is that essential value is independent of reinforcer magnitude. This assumption has been generally supported in studies of opioid self-administration in monkeys, but has not yet been investigated in rats. For example, Winger et al., (1996) allowed monkeys to self-administer four different doses of alfentanil or nalbuphine and found that elasticity of demand for these opioids did not differ by dose. Similarly, Winger et al. (2006) tested three doses of remifentanil in monkeys and also found that demand elasticity was independent of dose. While the dose independence of opioid demand elasticity has not yet been investigated in rats, there is some evidence with cocaine suggesting that results in monkeys may generalize to rats. Winger et al. (1993, 2006) tested three cocaine doses in monkeys and found that demand elasticity for the two larger doses did not differ, but demand for the lowest dose was more elastic. Kearns and Silberberg (2016) tested three doses of cocaine – 0.11, 0.33, and 1.0 mg/kg – in rats and found that elasticity of demand did not differ for the two larger doses. Demand for the small dose (near to the smallest dose that still acts as a reinforcer) was more elastic than was demand for the other doses. Thus, it appears that in both monkeys and rats, elasticity of demand for cocaine is dose-independent above a threshold dose, whereas in monkeys demand for opioids is dose-independent across all doses. Future research will be needed to determine whether elasticity of demand for opioids and for saccharin in rats is independent of reinforcer magnitude, as assumed by the exponential demand model.

Use of different heroin or saccharin magnitudes of reinforcement might have resulted in different results in the choice phases of the current study. There are seemingly conflicting

outcomes regarding the role of dose from previous studies investigating rats' choice between drugs and non-drug alternatives. Lenoir et al. (2013) allowed rats to choose between 20-s access to 0.2% saccharin (the same saccharin reinforcer used here) and one of three different doses of heroin (0.005, 0.01, and 0.02 mg/kg/infusion). They found that dose had no effect on preference. In another study investigating preference between cocaine and saccharin (again 0.2%, 20-s access), Cantin et al. (2010) tested three doses of cocaine (0.25 mg, 0.75 mg, and 1.5 mg) and found that dose did not affect preference. In contrast, Thomsen et al. (2013, 2014) found that rats' choice between cocaine and 75 μ l of vanilla-flavored Ensure diluted in water was dose dependent. A possible explanation for this discrepancy across studies is that 20 s of access to 0.2% saccharin may be such a large or powerful alternative reinforcer that its effects on behavior overshadow the effects of changes in dose in the majority of rats. It could be that watered-down Ensure is a relatively weaker reinforcer which permits the effects of cocaine dose manipulations on choice behavior to be seen. Future studies that vary the dose of heroin as well as the concentration or amount of saccharin could provide important information about how preference is affected by the magnitudes of the drug and non-drug alternatives available.

In addition to the reinforcer magnitude considerations discussed above, different methods of manipulating unit price might have produced different outcomes (e.g., see Nader et al., 1993). In the present study, unit price was manipulated only by varying the cost (number of lever presses per reinforcer). It is also possible to manipulate price by holding cost constant and varying the dose of heroin or amount of saccharin delivered. Whether this alternative method of manipulating price would result in similar findings regarding the essential values of heroin and saccharin is a question for future research.

A more general caveat regarding the interpretation of the results of the present study and similar studies investigating reinforcer value or preference is that the value of a reinforcer is relative to its surrounding conditions. Thus, our description of heroin preferers and saccharin preferers must be qualified by specifying that these terms apply within the context of the specific procedures used. Further, the present study focused on essential value and therefore investigated own-price elasticity of demand. But demand for a reinforcer may also vary as a function of the prices of other available reinforcers. A study investigating cross-price elasticity of demand for heroin and for saccharin could provide additional important information. For example, heroin could act as a substitute for saccharin and individual differences in the substitutability of heroin for saccharin (i.e., heroin's cross-price demand elasticity) may better reflect individual differences in addiction-like behavior than the essential value or preference measures used here. Future research into the interrelationships among own-price demand elasticity, cross-price demand elasticity, and preference could yield additional insights into addiction-like behavior in rats.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Ahmed SH. Validation crisis in animal models of drug addiction: Beyond non-disordered drug use toward drug addiction. *Neurosci. Biobehav. Rev.* 2010; 35:172–84. [PubMed: 20417231]
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. Royal. Stat. Soc.* 1995; 57:289–300.
- Bentzley BS, Fender KM, Aston-Jones G. The behavioral economics of drug self-administration: A review and new analytical approach for within-session procedures. *Psychopharmacol.* 2013; 226:113–125.
- Bentzley BS, Zhou TC, Aston-Jones G. Economic demand predicts addiction-like behavior and therapeutic efficacy of oxytocin in the rat. *Proc. Natl. Acad. Sci.* 2014; 111:11822–11827. [PubMed: 25071176]
- Cantin L, Lenoir M, Augier E, Vanhille N, Dubreucq S, Serre F, Vouillac C, Ahmed SH. Cocaine is low on the value ladder of rats: Possible evidence for resilience to addiction. *PLoS One.* 2010; 5:e11592. [PubMed: 20676364]
- Christensen CJ, Silberberg A, Hursh SR, Huntsberry ME, Riley AL. Essential value of cocaine and food in rats: Tests of the exponential model of demand. *Psychopharmacol.* 2008a; 198:221–229.
- Christensen CJ, Silberberg A, Hursh SR, Roma PG, Riley AL. Demand for cocaine and food over time. *Pharmacol. Biochem. Behav.* 2008b; 91:209–216. [PubMed: 18692088]
- Christensen CJ, Kohut SJ, Handler S, Silberberg A, Riley AL. Demand for food and cocaine in Fischer and Lewis rats. *Behav. Neurosci.* 2009; 123:165–171. [PubMed: 19170441]
- Colantuoni C, Rada P, McCarthy J, Patten C, Avena NM, Chadeayne A, Hoebl BG. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes. Res.* 2002; 10:478–488. [PubMed: 12055324]
- Feltoch N. Critical values for the robust rank-order test. *Commun. Stat. Simul. Comput.* 2005; 34:525–547.
- Galuska CM, Banna KM, Willse LV, Yahyavi-Firouz-Abadi N, See RE. A comparison of economic demand and conditioned-cued reinstatement of methamphetamine or food-seeking in rats. *Behav. Pharm.* 2011; 22:312.
- Grebenstein PE, Burroughs D, Roiko SA, Pentel PR, LeSage MG. Predictors of the nicotine reinforcement threshold, compensation, and elasticity of demand in a rodent model of nicotine reduction policy. *Drug Alcohol Depend.* 2015; 151:181–193. [PubMed: 25891231]
- Green A, Kaul A, O'Shea J, Sharma E, Bennett L, Mullings EL, Munafo MR, Nutt DJ, Melichar JK, Donaldson LF. Opiate agonists and antagonists modulate taste perception in opiate-maintained and recently detoxified subjects. *J. Psychopharmacol.* 2013; 27:265–275. [PubMed: 23364815]
- Hofford RS, Beckmann JS, Bardo MT. Rearing environment differentially modulates cocaine self-administration after opioid pretreatment: A behavioral economic analysis. *Drug Alcohol Depend.* 2016; 167:89–94. [PubMed: 27511893]
- Hursh SR, Silberberg A. Economic demand and essential value. *Psych. Rev.* 2008; 115:186–98.
- Hursh, SR. Behavioral economics and the analysis of consumption and choice. In: McSweeney, FK., Murphy, ES., editors. *The Wiley Blackwell Handbook of Operant and Classical Conditioning*. Wiley; Hoboken, NJ: 2014. p. 275-305.
- Huskinson SL, Naylor JE, Townsend EA, Rowlett JK, Blough BE, Freeman KB. Self-administration and behavioral economics of second-generation synthetic cathinones in male rats. *Psychopharmacol.* 2017; 234:589.
- Jain R, Mukherjee K, Singh R. Influence of sweet tasting solutions on opioid withdrawal. *Brain Res. Bull.* 2004; 64:319–322. [PubMed: 15561466]

- Kearns DN, Kim JS, Tunstall BJ, Silberberg A. Essential values of cocaine and non-drug alternatives predict the choice between them. *Addict. Biol.* 2016; doi: 10.1111/adb.12450
- Kearns DN, Silberberg A. Dose and elasticity of demand for self-administered cocaine in rats. *Behav. Pharmacol.* 2016; 27:289–292. [PubMed: 26866971]
- Kerstetter KA, Ballis MA, Duffin-Lutgen S, Carr AE, Behrens AM, Kippin TE. Sex differences in selecting between food and cocaine reinforcement are mediated by estrogen. *Neuropsychopharmacol.* 2012; 37:2605–2614.
- Koffarnus MN, Woods JH. Individual differences in discount rate are associated with demand for self-administered cocaine, but not sucrose. *Addict. Biol.* 2013; 18:8–18. [PubMed: 21812874]
- Lamb RJ, Daws LC. Ethanol self-administration in serotonin transporter knockout mice: Unconstrained demand and elasticity. *Genes Brain Behav.* 2013; 12:741–747. [PubMed: 23927813]
- Lemley SM, Kaplan BA, Reed DD, Darden AC, Jarmolowicz DP. Reinforcer pathologies: Predicting alcohol related problems in college drinking men and women. *Drug Alcohol Depend.* 2016; 167:57–66. [PubMed: 27515726]
- Lenoir M, Ahmed SH. Supply of a nondrug substitute reduces escalated heroin consumption. *Neuropsychopharmacol.* 2008; 33:2272–2282.
- Lenoir M, Cantin L, Vanhille N, Serre F, Ahmed SH. Extended heroin access increases heroin choices over a potent nondrug alternative. *Neuropsychopharmacol.* 2013; 38:1209–1220.
- Madsen HB, Ahmed SH. Drug versus sweet reward: Greater attraction to and preference for sweet versus drug cues. *Addict. Biol.* 2015; 20:433–444. [PubMed: 24602027]
- Martin TJ, Smith JE, Dworkin SI. Training dose and session time as contextual determinants of heroin self-administration in rats. *Pharmacol. Biochem. Behav.* 1998; 60:415–421. [PubMed: 9632224]
- Nader MA, Hedeker D, Woolverton WL. Behavioral economics and drug choice: Effects of unit price on cocaine self-administration by monkeys. *Drug Alcohol Depend.* 1993; 33:193–199. [PubMed: 8261883]
- National Academy of Sciences. Guide for the Care and Use of Laboratory Animals. National Academy Press; Washington, DC: 2011.
- Pecina S, Berridge KC. Central enhancement of taste pleasure by intraventricular morphine. *Neurobiol.* 1994; 3:269–280.
- Siegel, S., Castellan, NJ. Nonparametric statistics for the behavioral sciences. McGraw-Hill; New York: 1988.
- Smith KS, Berridge KC. Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. *J. Neurosci.* 2007; 27:1594–1605. [PubMed: 17301168]
- Thomsen M, Caine SB. Chronic intravenous drug self-administration in rats and mice. *Curr. Protocol. Neurosci.* 2005:9–20.
- Thomsen M, Barrett AC, Negus SS, Caine SB. Cocaine versus food choice procedure in rats: environmental manipulations and effects of amphetamine. *J. Exp. Anal. Behav.* 2013; 99:211–233. [PubMed: 23319458]
- Thomsen M, Fulton BS, Caine SB. Acute and chronic effects of the M1/M4-preferring muscarinic agonist xanomeline on cocaine vs. food choice in rats. *Psychopharmacol.* 2014; 231:469–479.
- Tunstall BJ, Kearns DN. Reinstatement in a cocaine versus food choice situation: reversal of preference between drug and non-drug rewards. *Addict. Biol.* 2013; 19:838–48. [PubMed: 23551949]
- Tunstall BJ, Kearns DN. Cocaine can generate a stronger conditioned reinforcer than food despite being a weaker primary reinforcer. *Addict. Biol.* 2014; 21:282–293. [PubMed: 25363637]
- Tunstall BJ, Kearns DN. Sign-tracking predicts increased choice of cocaine over food in rats. *Behav. Brain. Res.* 2015; 281:222–228. [PubMed: 25541036]
- Tunstall BJ, Riley AL, Kearns DN. Drug specificity in drug versus food choice in male rats. *Exp. Clin. Psychopharm.* 2014; 22:364–372.
- Vandaele Y, Cantin L, Serre F, Vouillac-Mendoza C, Ahmed SH. Choosing under the influence: A drug-specific mechanism by which the setting controls drug choices in rats. *Neuropsychopharmacol.* 2015; 41:646–657.

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- Vanhille N, Belin-Rauscent A, Mar AC, Ducret E, Belin D. High locomotor reactivity to novelty is associated with an increased propensity to choose saccharin over cocaine: new insights into the vulnerability to addiction. *Neuropsychopharmacol.* 2015; 40:577–589.
- Winger G. Fixed-ratio and time-out changes on behavior maintained by cocaine or methohexital in rhesus monkeys: I. Comparison of reinforcing strength. *Exp. Clin. Psychopharmacol.* 1993; 1:142–153.
- Winger G, Woods JH, Hursh SR. Behavior maintained by alfentanil or nalbuphine in rhesus monkeys: Fixed-ratio and time-out changes to establish demand curves and relative reinforcing effectiveness. *Exp. Clin. Psychopharmacol.* 1996; 4:131–140.
- Winger G, Galuska CM, Hursh SR, Woods JH. Relative reinforcing effects of cocaine, remifentanil, and their combination in rhesus monkeys. *J. Pharmacol. Exp. Ther.* 2006; 318:223–229. [PubMed: 16571623]

Highlights

- Rats' demand for heroin was more elastic than their demand for saccharin.
- The essential value of heroin predicted subsequent choice of heroin over saccharin.
- The essential value of saccharin was unrelated to preference.
- Increased heroin access made demand for both heroin and saccharin less elastic.
- Similar exposure to saccharin did not alter these reinforcers' demand elasticity.

Figure 1.
Schematic diagram of sequence of phases.

Figure 2.

a: Group mean numbers of heroin infusions (filled circles) and saccharin reinforcers (open squares) earned at each FR plus demand curves fit by the exponential model.

b: Normalized consumption as a function of normalized price as well as normalized demand curves fit by the model.

c: Mean ($\pm$ SEM) essential value of heroin (black bar) and saccharin (white bar). ** indicates $p < 0.01$.

Figure 3.

a: Percent choice of heroin averaged over criterion sessions for individual subjects. The horizontal line represents group mean preference.

b: Mean ($\pm$ SEM) percent choice of heroin at each saccharin FR. The FR for heroin was always 1.

c: Scatter plot and best-fit line showing relationship between heroin's essential value and percent choice of heroin.

d: Scatter plot and best-fit line showing relationship between saccharin's essential value and percent choice of heroin. * indicates $p < 0.05$. ** indicates $p < 0.01$

Figure 4. Mean ($\pm$ SEM) essential value of heroin and saccharin for heroin preferers (black bars) and saccharin preferers (white bars). * indicates $p < 0.05$

Essential Value Before and After Increased-Access Sessions

Figure 5. Mean ($\pm$ SEM) essential value of heroin (black bars) and saccharin (white bars) before and after the increased-access phase for the Heroin group (left of dashed line) and the Saccharin group (right of dashed line). ** indicates $p < 0.01$