Pharmacology, Biochemistry and Behavior 184 (2019) 172744

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Reduced ethanol self-administration in rats produced by the introduction of a high value non-drug alternative reinforcer

Jung S. Kim*, David N. Kearns

American University, United States of America

ARTICLE INFO

Keywords:
Ethanol
Demand elasticity
Sucrose
Non-drug alternative reinforcers
Rats

ABSTRACT

Previous studies have shown that providing rats with a non-drug alternative in a choice situation can reduce ethanol taking in rats. There is also evidence that brief experience with non-drug reinforcers can reduce the reinforcing effects of drugs like cocaine, even when those non-drug alternatives are not pitted against the drug in a choice procedure. The goal of the present experiment was to determine whether experience with sucrose – a high value non-drug reinforcer in rats – in a non-choice situation would reduce ethanol's reinforcing effects, as measured within a behavioral economic framework. In a first phase, separate groups of rats worked on fixed-ratio schedules for ethanol, sucrose, or ethanol plus sucrose (during separate components within a session). In a second phase, all rats worked for ethanol and sucrose during alternating components. The introduction of sucrose components in the second phase to the group that previously only had experience with ethanol caused a significant decrease in ethanol self-administration. There was also a significant interaction whereby the effect of phase on the elasticity of demand for ethanol differed between the group that only had ethanol and the group that had ethanol plus sucrose in the first phase. These results indicate that a high value non-drug alternative reinforcer can reduce ethanol's reinforcing effects even when that alternative is not available at the time when ethanol is available. These findings suggest that treatments aiming to increase exposure to non-alcohol sources of reinforcement might be beneficial in reducing alcohol drinking.

1. Introduction

A number of recent studies have shown that ethanol taking in rats can be reduced by giving subjects a choice between ethanol and a non-drug alternative reinforcer, like saccharin (Augier et al., 2018; Pelloux and Baunez, 2017; Russo et al., 2018). These studies employed a discrete-trials choice procedure where rats made a limited number of mutually exclusive choices between ethanol and the non-drug alternative. A reduction in ethanol taking under conditions where the operant behavior leading to the non-drug alternative directly competes with the behavior leading to ethanol is an expected outcome, provided the non-drug alternative is of sufficient value to compete with ethanol for a share of behavior. Similar reductions in drug taking in situations where choosing the non-drug alternative precludes taking the drug have been observed with cocaine (e.g., Cantin et al., 2010), heroin (Lenoir et al., 2013), nicotine (Huynh et al., 2017) and other substances.

More unexpected, perhaps, is the observation that experience with non-drug reinforcers may reduce the reinforcing effects of drugs even when the alternatives are not pitted directly against drugs in a choice situation. For example, environmental enrichment studies, where animals are given access to toys, running wheels, or social interaction in the homecage, show that exposure to non-drug reinforcers can reduce the rewarding effects of drugs even when those non-drug alternatives are not available in the test chamber while subjects are working for the drug (Deehan Jr et al., 2011; Stairs and Bardo, 2009; Yates et al., 2019). In environmental enrichment studies, animals are often exposed to multiple sources of non-drug reinforcement in the homecage for 24 h per day from weaning to adulthood. However, shorter periods of access to a single non-drug alternative reinforcer may also alter the reinforcing effects of drugs. Liu and Grigson (2005) found that just 5 min of access to a sweet solution in the homecage reduced subsequent cocaine seeking in the self-administration chamber (see also Lenoir and Ahmed, 2008, for a similar result). As with the environmental enrichment effect, the reduced drug seeking observed in Liu and Grigson's study appears to be due to a fundamental change in the experience of the drug, rather than to the kind of response competition that may lead to reduced drug taking in mutually exclusive choice procedures.

The primary goal of the present experiment was to test whether experience working for a potent non-drug reinforcer – sucrose – would

* Corresponding author at: 10550 North Torrey Pines Road, La Jolla, CA 92037, United States of America.
E-mail address: jskim@scripps.edu (J.S. Kim).

https://doi.org/10.1016/j.pbb.2019.172744
Received 12 April 2019; Received in revised form 1 July 2019; Accepted 24 July 2019
Available online 25 July 2019
0091-3057/

reduce the reinforcing strength of ethanol in rats in a situation where they did not choose between these reinforcers. A behavioral economic framework was used so that the essential value (EV; Hursh and Silberberg, 2008) – a behavioral economic measure reflecting inelasticity of demand for a reinforcer – of ethanol could be evaluated. EV has been shown to be related to a number of addiction-related behaviors in animals and humans (e.g., Aston et al., 2015; Bentzley et al., 2014; Kearns et al., 2017; Lemley et al., 2016; O'Connor et al., 2016; Schwartz et al., 2017). One group of rats worked for ethanol only in an operant chamber during brief components on an ascending series of fixed-ratio (FR) schedules. A second group also worked for ethanol on ascending FR schedules, but ethanol components alternated with components where sucrose pellets were available on the same FR schedules. It was hypothesized that demand for ethanol would be more elastic in the group that had experience with sucrose. Symmetrically, this experiment investigated whether experience working for ethanol would alter the elasticity of demand for sucrose. A third group that only worked for sucrose was compared to the group that worked for ethanol and sucrose in alternating components. In a final phase of the experiment, the groups that previously worked for only one of the reinforcers were given access to the other to determine whether the introduction of a new reinforcer would affect the value of the familiar reinforcer.

2. Methods

2.1. Subjects

All procedures were approved by American University's Institutional Animal Care and Use Committee. Subjects were treated in accordance with the guide for the Care and Use of Laboratory Animals (National Academy of Sciences, 2011) throughout the study. Twenty five male Long-Evans rats were acquired from Harlan Sprague Dawley when they were ~120 days old. Rats weighed ~350 g at the start of the experiment. Rats were individually housed in OptiRat Plus housing bins (38.9 × 56.9 × 26 cm, 1181 sq. cm) where they had ad lib access to rat chow and water.

2.2. Apparatus

Operant sessions took place in standard Med-Associates rat operant chambers equipped with stimulus lights, a food dispenser, a food receptacle, syringe pump, retractable response levers, a speaker for producing a tone stimulus (4000 Hz/85 dB) and a white noise stimulus (85 dB). Stimulus presentation, reinforcement delivery, and response recording were controlled using a program written and executed with Med-Associates software. The operant chambers were located within larger attenuation chambers that attenuate both light and sound. The attenuation chambers each had a single exhaust fan built into their walls that kept fresh air circulating during training sessions in addition to providing a masking noise.

2.3. Procedure

2.3.1. Induction of ethanol drinking

Prior to beginning operant training, rats were induced to drink ethanol in their homecages using an intermittent access regimen similar to the intermittent access two-bottle choice procedure, which has been shown to produce relatively high levels of unsweetened ethanol drinking in rats within a few weeks (Carnicella et al., 2014). At 12:00 pm on Mondays, Wednesdays, and Fridays, all rats were given 24 h access to a 50-ml bottle containing 20% ethanol (*v*/v, in tap water) for four weeks. Rats continued to have ad lib access to water during days of ethanol access.

2.3.2. Demand phase 1

Following the four weeks of ethanol drinking induction, rats were assigned to one of three groups, which were distinguished by the reinforcer(s) they were initially trained with during operant sessions: ethanol only (EO), sucrose only (SO), or ethanol and sucrose (E + S). Group assignment was made with the goal of matching groups as closely as possible with respect to average ethanol consumption during the previous induction phase. EO rats (n = 9) had access to one lever (left or right, counterbalanced) during operant sessions and pressing this lever resulted in the delivery of 0.1 ml of unsweetened ethanol (20% *v*/v, in water) delivered via syringe pump to the trough within the food receptacle. SO rats (n = 8) had access to one lever during operant sessions and pressing this lever resulted in delivery of a 45-mg sucrose pellet. E + S rats (n = 8) were trained to press one lever for 0.1-ml ethanol reinforcers and another lever for sucrose pellets during alternate components (only one lever was inserted at a time during these separate components).

Prior to beginning lever press training, rats were given two days to habituate to the operant chambers during 1 h per day for two days. No levers, reinforcers, or audiovisual cues were presented during these habituation sessions. Each experimental session during demand training was divided into eight 10-min components that were separated by a 5-min intercomponent interval, during which no levers were inserted into the chamber. The E + S group had four components of each type, presented in random order with the restriction that no more than two consecutive components were of the same type. The EO and SO groups had four reinforced components per session with their respective reinforcers, while the rest were dummy components during which no lever was inserted into the chamber. This was done in order to ensure that the EO and SO groups were matched to the E + S group in terms of session length and the number and distribution of components providing access to their reinforcer. Component presentation order was randomized from session to session, and each session lasted 2 h. Rats in all groups were initially trained with an FR-1 schedule operative during reinforced components. Each lever press resulted in delivery of a single sucrose pellet or 0.1-ml ethanol reinforcer followed by a 10-s timeout signaled by illumination of the cuelight above the lever and presentation of the tone or white noise (counterbalanced over rats in the EO and SO groups, and across reinforcers in the E + S groups). Lever presses during the timeout were recorded, but had no programmed consequences. After 28 sessions of training on this procedure with an FR-1 schedule, the ratio requirement increased every two sessions in the following manner: 2, 4, 8, 16, 32, and 64. Thus, rats had a total of 40 sessions during the first demand phase.

2.3.3. Demand phase 2

Following the first phase of demand training, sucrose and ethanol components replaced dummy components for the EO and SO rats, respectively. The lever not used in Phase 1 was inserted during the new reinforcer components for these groups. Deliveries of the new reinforcer were followed by a 10-s timeout signaled by illumination of the cuelight above the lever plus presentation of the auditory stimulus (tone or white noise) not used in Phase 1. Aside from the introduction of sucrose/ethanol components to rats that had no experience with those reinforcers up until this point, all other aspects of demand training (i.e., component length, etc.) were the same as in Phase 1. The E + S group simply re-experienced the same demand procedure used in Phase 1. Because rats' response rates generally fell to low levels during the high FRs of Phase 1, all rats received 12 sessions on FR 1 with both reinforcers in order to allow them to re-acquire the lever-press operant before the response ratios were incremented according to the same sequence (FR 2, 4, 8, 16, 32, 64) used in the first demand phase. Thus, rats had 24 sessions during the second demand phase.

2.3.4. Data analysis

For the demand data, the numbers of ethanol and sucrose reinforcers earned were averaged over the training sessions at each FR (for FR 1, the mean of the last two sessions was used). Individual

subjects' data were fit by Hursh and Silberberg's (2008) exponential-demand equation:

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

where Q is quantity of reinforcers earned, Q_0 is reinforcers earned as price approaches 0, k is a constant defining the range of reinforcers earned in log units ($k = 2.4$ here, the largest range observed for any individual or group mean), α determines the rate of decline in reinforcers earned, and C is cost (FR size).

The primary measure of interest from the demand phase was essential value (EV), which is inversely related to α and reflects inelasticity of demand. EVs of ethanol and sucrose were calculated for each subject according the formula given by Hursh (2014):

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

For all statistical tests, the Type 1 error rate was set to 0.05. Repeated measures or mixed ANOVAs were performed on ethanol consumed during the induction phase, ethanol or sucrose reinforcers earned across FRs during the demand phases, and EV scores derived from fits of the model to individual subjects' data. Group was a between-subjects factor and FR, Phase, or Week were within-subjects factors in ANOVAs.

3. Results

3.1. Induction

Fig. 1 presents mean ethanol consumption per day during the four weeks of intermittent access to ethanol in the homecage. During Week 1, all groups consumed about 2 g/kg/day ethanol and increased to about 4 g/kg/day by Week 4. Rats generally drank more on Mondays than on the other days. A mixed ANOVA indicated that there were significant main effects of Week ($F[3,66] = 9.9, p < 0.001$) and Day of the Week ($F[2,44] = 11.1, p < 0.001$), but no main effect of Group ($F < 1$). There were no significant interactions involving any of these variables (all $Fs \leq 2.1$, all $ps \geq 0.05$).

3.2. Ethanol demand

Five rats (3 from the EO group and 2 from the E + S group) failed to acquire the lever press response within 28 acquisition sessions and were excluded from further training. None of these rats' data were included in statistical analyses. The number of remaining rats per group was as follows: E + S group, $n = 6$; EO group, $n = 6$; and SO group, $n = 8$. For the second demand phase, 2 rats in the SO group and 1 rat in the EO group earned an average of less than one ethanol reinforcer per session at all FRs. This meant that demand curves could not be fitted to their data and therefore they had no ethanol EV scores for the second demand phase. These rats' ethanol demand data (reinforcers earned and EV scores) from both phases was excluded from analyses.

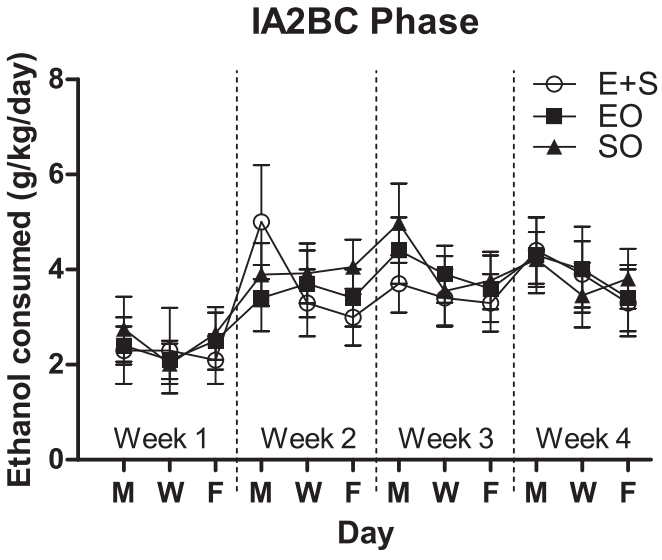

Fig. 1. Mean (± SEM) ethanol consumed in the homecage on each Monday (M), Wednesday (W), and Friday (F) 24-h ethanol access period during each of the four weeks of the induction period for the E + S (circles), EO (squares), and SO (triangles) groups.

Fig. 2 presents mean numbers of ethanol ratios completed (reinforcers earned) at each FR and the total collapsed across FRs during the first and second demand phases for the E + S and EO groups and during the second phase for the SO group (the SO group did not have ethanol components during the first phase). During the first phase, ethanol reinforcers earned were quite similar for the E + S and EO groups across FRs, beginning at about 20 ethanol reinforcers at FR 1 and declining to about one reinforcer at FR 32. Compared to the first determination, the EO group completed consistently fewer ethanol ratios during the second demand determination whereas this pattern was not observed for the E + S group. The SO group was comparable to the EO group in terms of ethanol consumption during the second demand phase.

Statistical analyses confirmed these impressions. For the E + S and EO groups, which both had ethanol components in both phases, a 2 × 2 × 7 (Group × Phase × FR) mixed ANOVA was performed on their ethanol consumption data. There was a significant Group × Phase interaction ($F[1,9] = 12.2, p < 0.01$) and a significant main effect of FR ($F[6,54] = 20.3, p < 0.001$). No other main effects or interactions were significant (all $Fs \leq 1.7$, all $ps > 0.10$). To resolve the significant Group × Phase interaction, 2 × 7 (Phase × FR) repeated measures ANOVAs were performed for the E + S and EO groups separately. There was a significant effect of Phase for the EO group ($F[1,4] = 18.4, p < 0.05$), but not for the E + S group ($F[1,5] = 4.2, p > 0.05$). The effect of FR was significant for both groups (both $Fs \geq 9.2$, both $ps < 0.001$), but there was no Phase × FR interaction in either group (both $Fs \leq 1.7$, both $ps \geq 0.15$). A 3 × 7 (Group × FR) ANOVA was performed on the ethanol ratios completed data from the second phase, where all three groups worked for ethanol. There was no significant effect of Group ($F[2,14] = 1.3, p > 0.25$) or significant Group × FR interaction ($F < 1$), but there was a significant effect of FR ($F[6,84] = 22.7, p < 0.001$).

The left panel of Fig. 3 presents mean ethanol EV for the E + S and EO groups from both phases and from Phase 2 for the SO group. Ethanol EV was comparable across the E + S and EO groups in Phase 1. Ethanol EV increased slightly for the E + S group in Phase 2, but decreased slightly for the EO group in Phase 2. Ethanol EV in the SO group was about comparable to that of the EO group in Phase 2. The right panel of Fig. 3 shows that the mean change in ethanol EV across phases was positive for the E + S group, but negative for the EO group. Table 1 presents individual subjects' EV scores from both phases and the associated difference scores (Phase 2 EV – Phase 1 EV).

A 2 × 2 (Group × Phase) mixed ANOVA performed on the E + S and EO groups' ethanol EV scores confirmed that there was a significant Group × Phase interaction ($F[1,9] = 2.1, p < 0.05$), but there were no main effects of Phase or Group (both $Fs < 1$). To explore this interaction further, paired-samples t-tests were used to compare Phase 1 ethanol EV to Phase 2 EV in each of the groups separately. Neither comparison was significant (E + S group: $t[5] = 1.9, p > 0.10$; EO group: $t[4] = -1.7, p > 0.15$). However, the mean EV difference score over phases (Phase 2 – Phase 1) was significantly higher in the E + S group than in the EO group (independent samples t-test, $t[9] = 2.4, p < 0.05$). This difference reflects the significant Phase × Group interaction. A one-way ANOVA performed on all groups' ethanol EV scores from the second phase was not significant ($F[2,16] = 1.3, p > 0.3$).

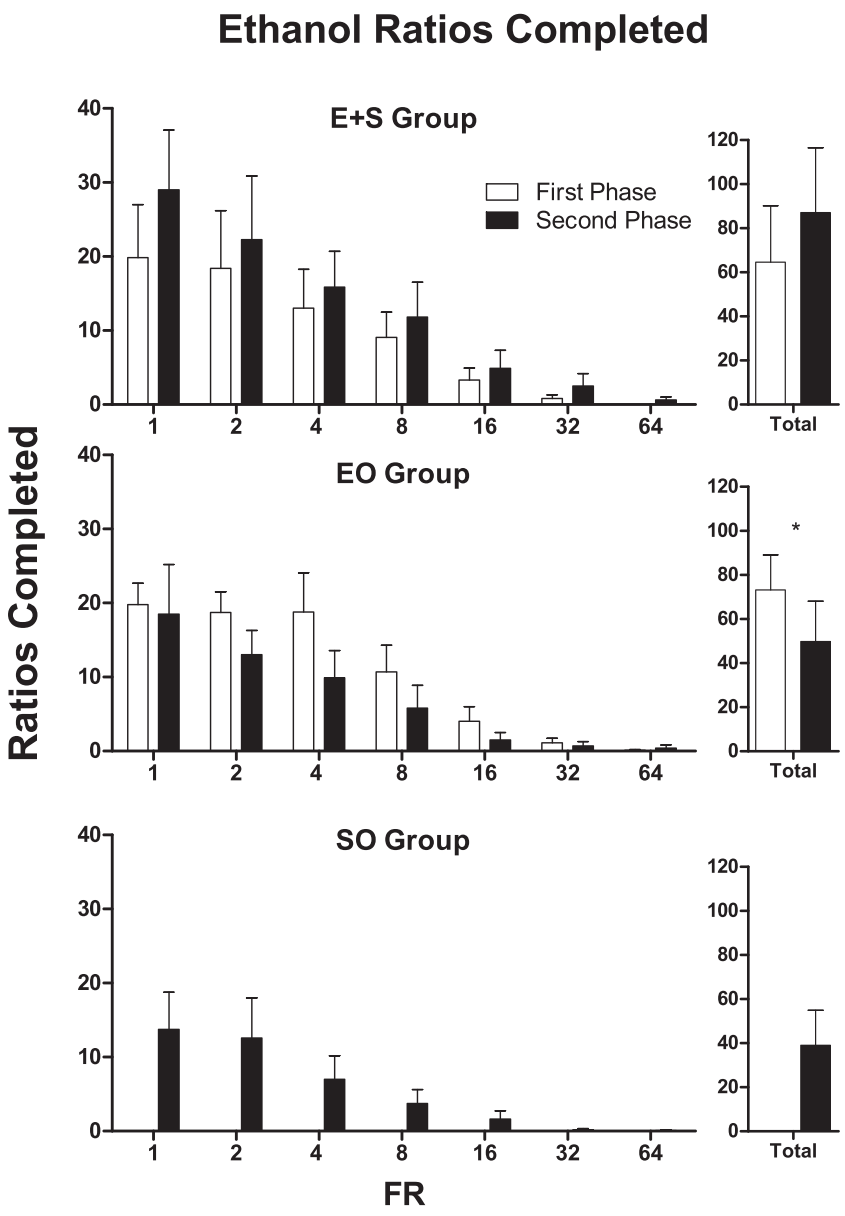

Fig. 2. Mean (± SEM) ethanol reinforcers earned in the operant chamber at each fixed ratio (FR) tested plus total ethanol reinforcers earned across FRs during the first (top panel) and second (bottom panel) demand phases for the E + S (white bars), EO (black bars), and SO (striped bars) groups. The SO group only had ethanol components during the second demand phase.

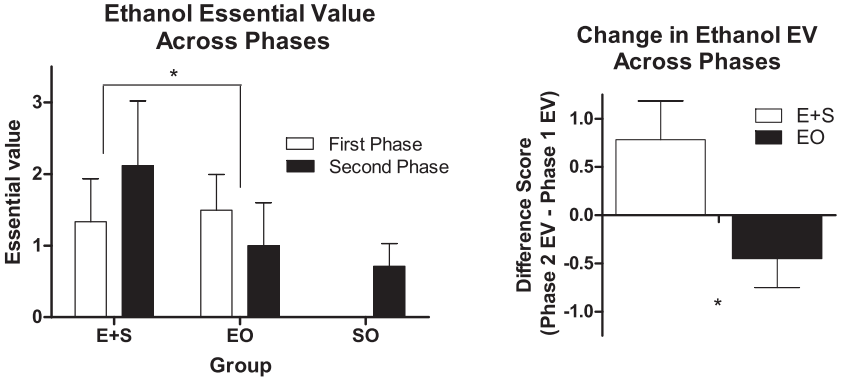

Fig. 3. Left panel: mean (± SEM) ethanol essential value (EV), derived from fits of the exponential demand model to individual subjects' data, across the first and second demand phases for each group. * indicates Group × Phase interaction significant at $p < 0.05$. Right panel: mean (± SEM) difference (Phase 2 – Phase 1) in EV across phases for the E + S and EO groups. The SO group is not represented because they did not have ethanol components in the first demand phase. * indicates $p < 0.05$.

Table 1
Essential values (EVs) of ethanol and sucrose across phases, as well as EV difference scores (Phase 2 EV – Phase 1 EV) for individual subjects.

Ethanol					Sucrose		
Group	Subject	EV phase 1	EV phase 2	Difference	EV phase 1	EV phase 2	Difference
E+S	3	2.7	5.5	2.7	15.3	18.6	3.4
	24	0.1	0.1	0.0	21.8	17.0	−4.8
	5	0.3	0.2	−0.2	4.2	5.1	0.8
	6	0.9	1.9	1.0	1.3	2.7	1.5
	1	0.5	0.9	0.4	1.2	3.2	2.1
	13	3.4	4.2	0.8	8.0	13.9	5.8
	Mean	**1.3**	**2.1**	**0.8**	**8.6**	**10.1**	**1.5**
	SD	**1.4**	**2.2**	**1.0**	**8.3**	**7.2**	**1.4**
EO	11	2.9	3.2	0.3	–	16.8	–
	14	2.1	0.8	−1.3	–	3.9	–
	19	0.4	0.2	−0.2	–	3.6	–
	4	1.0	0.6	−0.4	–	1.6	–
	7	[a]	[a]	[a]	–	0.3	–
	28	1.1	0.4	−0.7	–	1.6	–
	Mean	**1.5**	**1.0**	**−0.4**	–	**4.6**	–
	SD	**1.0**	**1.2**	**0.6**	–	**6.1**	–
SO	2	–	0.1	–	4.4	3.9	−0.4
	29	–	1.8	–	18.0	25.0	7.1
	20	–	0.0	–	5.1	4.0	−1.1
	10	–	[a]	–	13.9	22.1	8.2
	30	–	0.6	–	6.6	6.1	−0.5
	22	–	[a]	–	2.0	2.4	0.4
	12	–	1.5	–	12.7	9.5	−3.2
	15	–	0.2	–	2.9	3.4	0.5
	Mean	–	**0.7**	–	**8.2**	**9.6**	**1.4**
	SD	–	**0.8**	–	**5.9**	**8.9**	**4.0**

SD = standard deviation.
[a] Indicates that a subject made too few responses to plot a demand curve.

3.3. Sucrose demand

Fig. 4 shows number of ratios completed when responding for sucrose during Phase 1 and Phase 2 for the E + S and SO groups and for the EO group during Phase 2 (the EO group did not have sucrose components during Phase 1). Sucrose pellets earned in both the E + S and SO groups decreased from about 60 pellets at the low FRs to less than five pellets as the FR increased to 64. The performance of the E + S and SO groups during Phase 2 was similar to that of their performance in Phase 1, except there was a slight but consistent increase in number of pellets earned at most FRs tested. The EO group appeared to earn fewer pellets than the other two groups, but due to relatively large variability in sucrose pellet consumption this was not a reliable difference.

A 2 × 2 × 7 (Group × Phase × FR) mixed ANOVA performed on the sucrose ratios completed data from the E + S and SO groups confirmed that there was a significant effect of Phase ($F[1,12] = 7.7$, $p < 0.05$) and FR ($F[6,72] = 47.1$, $p < 0.001$). No other main effects or interactions were significant (all $Fs \leq 1.2$, all $ps > 0.25$). A 3 × 7 (Group × FR) mixed ANOVA performed on all three groups' sucrose consumption data from the second phase indicated that there was only a significant effect of FR ($F[6102] = 50.8$, $p < 0.001$), but no effect of Group ($F[2,17] = 1.9$, $p > 0.15$) or Group × FR interaction ($F[12,102] = 1.7$, $p > 0.05$).

Fig. 5 shows group mean sucrose EV during the first and second phases. Table 1 presents data for individual subjects. Overall, sucrose EV, about 5–10 here, was much higher than ethanol EV (about 1–2, presented in Fig. 3). The E + S and SO groups were quite similar in terms of sucrose EV during both Phase 1 and 2. A 2 × 2 (Group × Phase) mixed ANOVA indicated that there was no main effect of Group ($F < 1$) or Phase ($F[1,12] = 1.9$, $p > 0.15$) and no interaction between these factors ($F < 1$). The EO group had somewhat lower sucrose EV than the other groups in Phase 2 but this difference was not

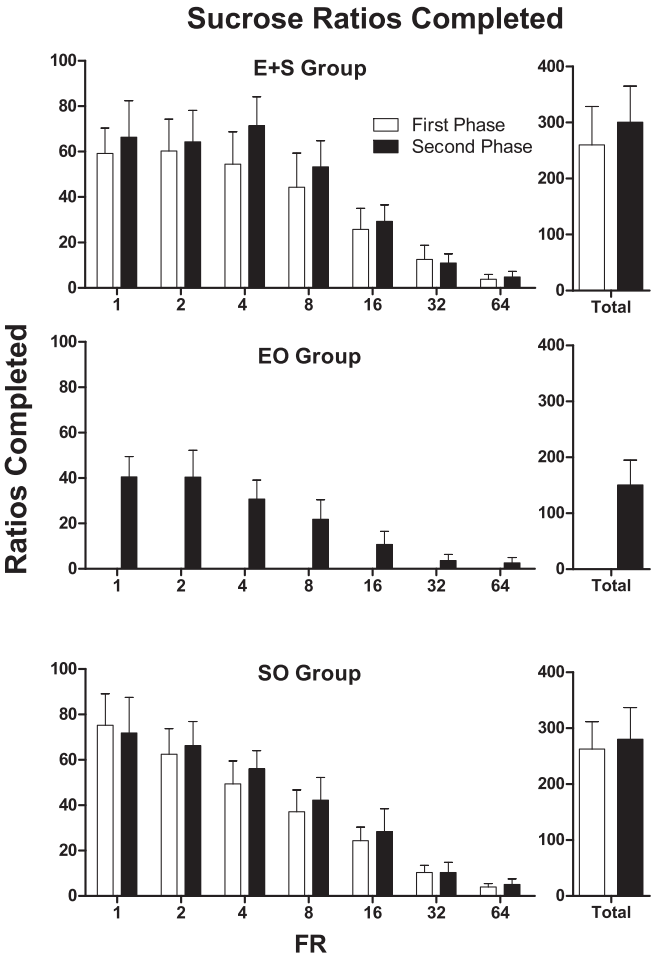

Fig. 4. Mean (± SEM) sucrose reinforcers earned in the operant chamber at each fixed ratios (FRs) tested plus total sucrose reinforcers earned across FRs during the first (top panel) and second (bottom panel) demand phases for the E + S (white bars), EO (black bars), and SO (striped bars) groups. The EO group only had sucrose components during the second demand phase.

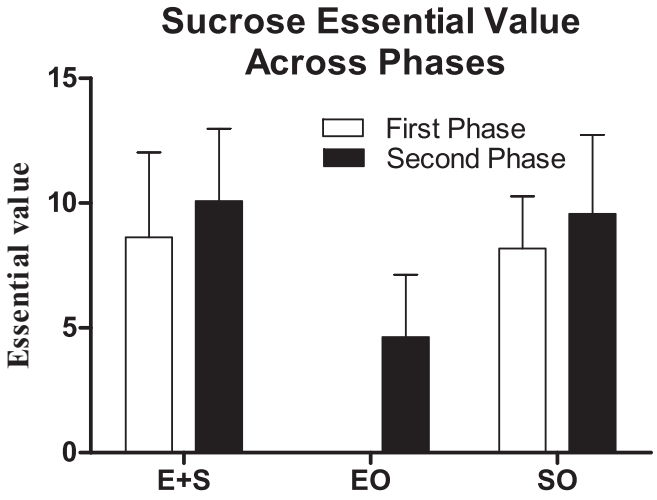

Fig. 5. Mean (± SEM) sucrose essential value (EV), derived from fits of the exponential demand model to individual subjects' data, across the first and second demand phases for each group.

statistically reliable (one-way ANOVA, $F < 1$).

4. Discussion

During the first demand phase, both ethanol self-administration and elasticity of demand (i.e., EV) for ethanol was quite similar for the E + S and EO groups. Alternating sucrose components thus do not appear to alter motivation for ethanol when rats are exposed to sucrose components from the outset of operant training. However, when sucrose components were introduced in Phase 2 to rats in the EO group, which previously only worked for ethanol, there was a significant decrease in ethanol self-administration. Further, for the E + S and EO groups, phase differently affected ethanol EV (i.e., there was a significant Phase × Group interaction). The finding that ethanol self-administration decreased upon the introduction of sucrose is consistent with the results of Liu and Grigson (2005) who first trained rats to self-administer cocaine alone before observing reduced cocaine seeking when a novel sweet solution was introduced briefly in the homecage. The present results and those of Liu and Grigson (2005) are also consistent with an earlier study by Carroll et al. (1989) who found that the change in availability (i.e., discontinuation or presentation) of a sweet solution in the operant chamber was an important factor affecting rats' cocaine self-administration. Similarly, Lenoir and Ahmed (2008) found that placement of food pellets on the floor of the operant chamber while rats worked for heroin made demand for heroin more elastic in rats that had prior extended-access heroin self-administration. It should be noted, however, that the Carroll et al. (1989) and Lenoir and Ahmed (2008) studies involved concurrent (though not mutually exclusive) access to the drug and the non-drug alternatives, whereas the present study and Liu et al. did not.

The main finding with respect to ethanol EV here was the significant Phase × Group interaction for the E + S and EO groups. Though there was no statistically significant change in ethanol EV across phases within either of these groups considered alone, the significant interaction appears to be as much due to an increase in ethanol EV in the E + S group as it is to a decrease in the EO group. In Phase 2, the E + S group was simply re-tested on the same demand procedures of Phase 1. It is not entirely clear why ethanol EV might have shown a tendency to increase with repeated testing. The EV of sucrose in the E + S group and in the SO group also slightly (but not significantly) increased when retested. It is possible that this is due to a kind of practice effect, where experiencing the ascending series of FRs makes rats more persistent over time. Perhaps using a less steeply increasing series of FRs would have prevented this tendency for EV to increase over time. It is interesting to note that out of four instances where the EV of a reinforcer was retested in Phase 2, the only case where there was no tendency for EV to increase was when ethanol EV was retested in the EO group. Though it cannot be said that the EV of ethanol significantly decreased in the EO group given statistical outcomes, it was the case that the effect of repeated testing on ethanol EV was different for the EO and E + S groups.

A limitation of the current study is the small final sample sizes. The initial sample sizes were 8, 9, and 8 for the E + S, EO, and SO groups, respectively. Due to failures to respond for ethanol at meaningful levels, several rats were excluded. The final sample sizes for the ethanol demand analyses for the E + S, EO, and SO groups were 6, 5, and 6, respectively. No rats had to be excluded for failure to lever press for sucrose. Previous studies have also reported exclusions of rats due to failure to acquire operant responding for ethanol, even when a form of ethanol sweetening was used (e.g., Mangieri et al., 2012; Samson et al., 2004). The failures of acquisition of lever pressing for ethanol, but not sucrose, in the present experiment are consistent with the finding the EV of ethanol (mean EV of approximately 1–2 across groups) was much lower than that of sucrose (mean EV of 5–10 across groups). It appears that for some rats, ethanol's value was too low to support much, if any, operant responding. The small final sample size of the EO group makes it especially difficult to draw firm conclusions about this group's sucrose results. Inspection of Figs. 4 and 5 shows that, though not significant, the EO group generally completed fewer ratios for sucrose and had lower sucrose EV than either of the other two groups. With more rats in the EO group, perhaps these differences would have been significant.

That the addition of sucrose, which was a relatively high value reinforcer compared to ethanol, reduced ethanol self-administration is reminiscent of incentive contrast studies (see Flaherty, 1982 for review). In perhaps the earliest known study of reward contrast, Tinklepaugh (1928) had monkeys perform an operant response for a piece of fruit. When monkeys expecting fruit were reinforced with lettuce instead, their operant behavior was severely disrupted. In contrast, without the expectation of fruit, lettuce was a perfectly acceptable reinforcer. Although the procedures of the present experiment differed much from ones typically used in incentive contrast experiments, the observation that introduction of a higher value reinforcer caused rats to work less hard for a low value reinforcer suggests that contrast or a similar process could be at work here.

It is unclear why a potential contrast effect was not observed if only the Phase 1 results are considered. That is, the E + S group had experience with both ethanol and sucrose in Phase 1, which may have been expected to lead to reward contrast, but they did not differ from the groups that only had one of these reinforcers available in Phase 1. It appears that the history of ethanol alone in the EO group was an important factor. Previous studies with other reinforcers have shown that prior histories with the reinforcers to be contrasted can determine whether or not a contrast effect is observed (Flaherty, 1982). In contrast to the reduction in ethanol self-administration upon the introduction of sucrose in the EO group, the introduction of ethanol to the SO group in Phase 2 did not alter sucrose self-administration. This is perhaps not surprising as positive contrast (an increase in the value of a high value reinforcer after experience with a lower value reinforcer) appears less likely to be observed than negative contrast under a variety of conditions (Flaherty, 1982).

That the EV of ethanol was lower than the EV of sucrose seemingly contrasts with the results of Petry and Heyman (1995) who found that demand for ethanol was less elastic than demand for liquid sucrose. Procedural differences across studies likely account for the diverging conclusions regarding differences in the elasticities of demand for ethanol and sucrose. First, unsweetened ethanol was used here, whereas Petry and Heyman used sweetened ethanol. It may be that the aversive orosensory properties of ethanol, if not masked by a sweetener, make demand for it relatively elastic. Second, Petry and Heyman assessed demand in a choice procedure, where rats had concurrent access to a sucrose solution and a sucrose + ethanol solution as the prices of these solutions were manipulated. It is perhaps not surprising that rats would work harder for sucrose + ethanol than for sucrose alone, as the former is a combination of two reinforcing substances whereas the latter is just one component of that combination.

It may be thought that post-prandial polydipsia (e.g., Falk, 1966) could have contributed to the results of the present study because in some conditions rats had alternating access to sucrose pellets and ethanol within the same session. If polydipsia contributed to results, greater ethanol self-administration would be expected in those conditions where ethanol and sucrose components alternated as compared to conditions where ethanol access did not alternate with sucrose components. However, in the present experiment the EO group drank less ethanol when ethanol components alternated with sucrose pellets (Phase 2) than when ethanol components were presented alone (Phase 1). Further, there was no difference in ethanol consumption in the first phase between the E + S group, which had alternating ethanol and sucrose components, and the EO group, which had only ethanol components. It is likely that the 5-min intercomponent intervals used here were not conducive to promoting post-prandial polydipsia. In studies investigating post-prandial polydipsia, post-food-pellet licking occurred mostly in the few seconds soon after pellet delivery (DeCarolis et al., 2003; Falk, 1966; Jacquet, 1972). For example, DeCarolis et al. found

that when a food pellet was delivered on a fixed-time 60-s schedule, lick rates peaked within 10–15 s of pellet delivery and fell to near zero about 30 s after pellet delivery. For rats in the present study, at least 5 min would have passed from pellet delivery to the first opportunity to work for ethanol.

Elasticity of demand for alcohol in humans has been associated with alcohol-related problems (e.g., Lemley et al., 2016). The finding here that introduction of a high value non-drug reinforcer reduced ethanol taking, even though the non-drug alternative is not available at times when ethanol is available, may have clinical implications. For example, the present result is consistent with research in humans showing that increased experience of non-alcohol reinforcement is associated with reduced drinking-related problems (Joyner et al., 2016). Perhaps introducing a high value non-drug alternative reinforcer to individuals wishing to abstain from alcohol could weaken alcohol's reinforcing effects just enough to help them achieve this goal. Some support for this suggestion comes from a human study where encouraging individuals to think about non-drug sources of reinforcement resulted in a significant reduction in heavy drinking among individuals reporting low baseline levels of alcohol-free reinforcement (Murphy et al., 2012). Actually experiencing non-drug reinforcement, rather than just thinking about it, might even produce stronger effects on drinking. There may be challenges in identifying and making available high value non-drug rewards, but meeting this challenge could be worth the effort.

Acknowledgement

This research was supported by Award Number DA037269 from the National Institute on Drug Abuse (NIDA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health. NIDA did not play a role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

References

Aston, E.R., Metrik, J., MacKillop, J., 2015. Further validation of a marijuana purchase task. Drug Alcohol Depend. 152, 32–38.
Augier, E., Barbier, E., Dulman, R.S., Licheri, V., Augier, G., Domi, E., Barchiesi, R., Farris, S., Nätt, D., Mayfield, R.D., Adermark, L., 2018. A molecular mechanism for choosing alcohol over an alternative reward. Science 360, 1321–1326.
Bentzley, B.S., Jhou, T.C., Aston-Jones, G., 2014. Economic demand predicts addiction-like behavior and therapeutic efficacy of oxytocin in the rat. Proc. Natl. Acad. Sci. 111, 11822–11827.
Cantin, L., Lenoir, M., Augier, E., Vanhille, N., Dubreucq, S., Serre, F., Vouillac, C., Ahmed, S.H., 2010. Cocaine is low on the value ladder of rats: possible evidence for resilience to addiction. PLoS One 5, e11592.
Carnicella, S., Ron, D., Barak, S., 2014. Intermittent ethanol access schedule in rats as a preclinical model of alcohol abuse. Alcohol 48, 243–252.
Carroll, M.E., Lac, S.T., Nygaard, S.L., 1989. A concurrently available nondrug reinforcer prevents the acquisition or decreases the maintenance of cocaine-reinforced behavior. Psychopharmacology 97, 23–29.
DeCarolis, N.A., Myracle, A., Erbach, J., Glowa, J., Flores, P., Riley, A.L., 2003. Strain-dependent differences in schedule-induced polydipsia: an assessment in Lewis and Fischer rats. Pharmacol. Biochem. Behav. 74, 755–763.
Deehan Jr., G.A., Palmatier, M.I., Cain, M.E., Kiefer, S.W., 2011. Differential rearing conditions and alcohol-preferring rats: consumption of and operant responding for ethanol. Behav. Neurosci. 125 (2), 184–193.
Falk, J.L., 1966. Schedule-induced polydipsia as a function of fixed interval length. J. Exp. Anal. Behav. 9, 37–39.
Flaherty, C.F., 1982. Incentive contrast: a review of behavioral changes following shifts in reward. Anim. Learn. Behav. 10, 409–440.
Hursh, S.R., 2014. Behavioral economics and the analysis of consumption and choice. In: McSweeney, F.K., Murphy, E.S. (Eds.), The Wiley-Blackwell Handbook of Operant and Classical Conditioning. John Wiley & Sons, Ltd, Hoboken, NJ.
Hursh, S.R., Silberberg, A., 2008. Economic demand and essential value. Psychol. Rev. 115, 186–198.
Huynh, C., Fam, J., Ahmed, S.H., Clemens, K.J., 2017. Rats quit nicotine for a sweet reward following an extensive history of nicotine use. Addict. Biol. 22, 142–151.
Jacquet, Y.F., 1972. Schedule-induced licking during multiple schedules. J. Exp. Anal. Behav. 17, 413–423.
Joyner, K.J., Pickover, A.M., Soltis, K.E., Dennhardt, A.A., Martens, M.P., Murphy, J.G., 2016. Deficits in access to reward are associated with college student alcohol use disorder. Alcohol. Clin. Exp. Res. 40, 2685–2691.
Kearns, D.N., Kim, J.S., Tunstall, B.J., Silberberg, A., 2017. Essential values of cocaine and non-drug alternatives predict the choice between them. Addict. Biol. 22, 1501–1514.
Lemley, S.M., Kaplan, B.A., Reed, D.D., Darden, A.C., Jarmolowicz, D.P., 2016. Reinforcer pathologies: predicting alcohol related problems in college drinking men and women. Drug Alcohol Depend. 167, 57–66.
Lenoir, M., Ahmed, S.H., 2008. Supply of a nondrug substitute reduces escalated heroin consumption. Neuropsychopharmacology 33, 2272–2282.
Lenoir, M., Cantin, L., Vanhille, N., Serre, F., Ahmed, S.H., 2013. Extended heroin access increases heroin choices over a potent nondrug alternative. Neuropsychopharmacology 38, 1209–1220.
Liu, C., Grigson, P.S., 2005. Brief access to sweets protect against relapse to cocaine-seeking. Brain Res. 1049, 128–131.
Mangieri, R.A., Cofresí, R.U., Gonzales, R.A., 2012. Ethanol seeking by Long Evans rats is not always a goal-directed behavior. PLoS One 7, e42886.
Murphy, J.G., Dennhardt, A.A., Skidmore, J.R., Borsari, B., Barnett, N.P., Colby, S.M., Martens, M.P., 2012. A randomized controlled trial of a behavioral economic supplement to brief motivational interventions for college drinking. J. Consult. Clin. Psychol. 80, 876–886.
National Academy of Sciences, 2011. Guide for the Care and Use of Laboratory Animals. National Academy Press, Washington, DC.
O'Connor, R.J., Heckman, B.W., Adkison, S.E., Rees, V.W., Hatsukami, D.K., Bickel, W.K., Cummings, K.M., 2016. Persistence and amplitude of cigarette demand in relation to quit intentions and attempts. Psychopharmacology 233, 2365–2371.
Pelloux, Y., Baunez, C., 2017. Targeting the subthalamic nucleus in a preclinical model of alcohol use disorder. Psychopharmacology 234, 2127–2137.
Petry, N.M., Heyman, G.M., 1995. Behavioral economics of concurrent ethanol-sucrose and sucrose reinforcement in the rat: effects of altering variable-ratio requirements. J. Exp. Anal. Behav. 64, 331–359.
Russo, M., Funk, D., Loughlin, A., Coen, K., Le, A.D., 2018. Effects of alcohol dependence on discrete choice between alcohol and saccharin. Neuropsychopharmacology 43, 1859–1866.
Samson, H.H., Cunningham, C.L., Czachowski, C.L., Chappell, A., Legg, B., Shannon, E., 2004. Devaluation of ethanol reinforcement. Alcohol 32, 203–212.
Schwartz, L.P., Kim, J.S., Silberberg, A., Kearns, D.N., 2017. Heroin and saccharin demand and preference in rats. Drug Alcohol Depend. 178, 87–93.
Stairs, D.J., Bardo, M.T., 2009. Neurobehavioral effects of environmental enrichment and drug abuse vulnerability. Pharmacol. Biochem. Behav. 92, 377–382.
Tinklepaugh, O.L., 1928. An experimental study of representative factors in monkeys. J. Comp. Psychol. 8, 197–236.
Yates, J.R., Bardo, M.T., Beckmann, J.S., 2019. Environmental enrichment and drug value: a behavioral economic analysis in male rats. Addict. Biol. 24, 65–75.