

Ethanol regulated preference in rats

Gene M. Heyman

Department of Psychology, Harvard University, 33 Kirkland Street, Cambridge, MA 02138, USA

Received July 28, 1992 / Final version April 2, 1993

Abstract. A series of experiments evaluated the determinants of preference for mixtures of ethanol plus sucrose relative to sucrose in rats. One dipper served 10% ethanol mixed with 10% sucrose, and the second dipper served 10% sucrose. Lever presses operated each dipper according to a variable-interval 5-s schedule. In three experiments the subjects were given pre-session meals of sucrose (2.5–20 ml) or sucrose (20 ml) plus chow (5 or 10 g). Pre-session meals decreased responding maintained by sucrose but not responding maintained by ethanol mixture. In two experiments body weight was varied from 85% to 125% of the initial free-feeding values. Increases in body weight, like pre-session meals, decreased responding reinforced by sucrose, but typically did not decrease responding reinforced by ethanol mixture. Throughout most of the study, ethanol consumption remained at about 1.25 ml per half hour session (3–4 g/kg per 30 min). For example, pre-session access to ethanol mixture decreased within-session ethanol consumption, but total consumption, counting both sources, remained about 1.25 ml/session. The within-session patterns of responding also differed. Responding reinforced by ethanol mix decreased as a function of ethanol consumption, whereas responding reinforced by sucrose was relatively constant throughout the session. The simplest explanation of the results is that ethanol's pharmacological consequences regulated preference.

Key words: Ethanol – Preference – Substitutability – Body weight – Calories – Sucrose – Animal model of ethanol preference – Alcohol – Choice – Variable-interval schedule – Concurrent schedule – Lever press – Rat

The set of experiments described in this report are part of a series of studies on preference for mixtures of ethanol plus sucrose in rats (Heyman and Oldfather 1992; Heyman 1993). The common procedural feature in these experiments is that one dipper serves 10% sucrose, and a

second, concurrently available, dipper serves 10% sucrose plus 10% ethanol. In the first study (Heyman and Oldfather 1992) the requirement (a variable-interval schedule) for the ethanol mixture was increased, while the requirement for sucrose remained unchanged. The basic finding was that preference did not shift to the sucrose solution. Instead, responding maintained by ethanol mixture either increased or stayed about the same. In contrast, when both dippers served sucrose, increases in the reinforcer requirement for one dipper simply shifted preference to the other dipper. A follow-up study (Heyman 1993), which used ratio rather than interval schedules, obtained a similar pattern of results. For example, increases in the response requirement for the ethanol mixture resulted in increases in responding so that ethanol consumption remained approximately constant, independent of the response requirement.

The simplest interpretation of these results is that the ethanol mixture provided reinforcing consequences that could not be obtained from the sucrose solution. For instance, if the reinforcing effects of the two solutions had been identical then the rats would have switched to the dipper with the less demanding schedule requirement (as they did when both dippers served sucrose). Conversely, in choice experiments in which the reinforcers markedly differed, for example, concurrent food and water (e.g. Rachlin et al. 1976; Hursh 1978; Green and Rachlin 1991), increases in the schedule requirement for one reinforcer failed to shift preference to the other reinforcer (as was the case with ethanol mixture and sucrose). Similar phenomena are discussed in economic texts, under the heading "consumer demand." According to economists, the degree to which changes in price affect changes in demand depends largely on the availability of substitutable commodities (e.g., Baumol and Blinder 1988; Mansfield 1982). For example, demand for a particular brand of aspirin is elastic, whereas demand for a one-of-a-kind drug treatment for a fatal disease is inelastic. In economic terms, then, demand for ethanol plus sucrose was inelastic, and sucrose was a poor substitute for ethanol plus sucrose. One of the purposes of the experi-

ments described in this paper was to explore why sucrose did not substitute for ethanol plus sucrose.

It is possible that sucrose failed to substitute for ethanol plus sucrose (referred to hereafter as "ethanol mix"), because of ethanol's pharmacological effects. To test this idea, feeding conditions were manipulated. For instance, in the experiments described in this report, the rats were given pre-session meals of either sucrose, sucrose and chow, or ethanol mix. If preference for ethanol mix was inelastic because of ethanol's pharmacological effects, then pre-session access to sucrose or chow might decrease responding maintained by sucrose more so than responding maintained by ethanol mix. Taking this reasoning one step further, depending on the degree to which sucrose substitutes for ethanol mix, it may be possible to arrange feeding conditions which decrease sucrose consumption but do not decrease ethanol-mix consumption. In contrast, if preference for ethanol mix was controlled by its caloric consequences or gustatory effects (e.g., taste), as suggested by some researchers (e.g., Dole 1986), then changes in feeding conditions should produce similar changes in the reinforcing efficacy of sucrose and of ethanol mix. Thus changes in relative response rate will be used to assess the degree to which the reinforcing effects of ethanol mix and sucrose solution differed.

General methods

Subjects

Six male, experimentally naive Wistar rats (Charles River Breeders, Wilmington, MA) served as subjects. At the start of the study the rats were approximately 3 months old and had free-feeding weights of 292–314 g. The rats were housed singly in a colony room that was illuminated 12 h a day (lights on at 7:00 a.m.). Chow (Purina) was presented in the home cage, just after the session, and in some experiments there was also pre-session servings of chow. Ethanol and sucrose were available during the experimental session. In the first two experiments, the rats were maintained at 85% of their free-feeding weights. In Experiments 3–6, greater amounts of food were provided and, as a result, body weights reached 115–125% of their initial, free-feeding values. In the home cage there was free access to water.

Apparatus and reinforcement contingencies

The experiments were conducted in three standard operant chambers (MED Associates: 28 cm, 20.5 cm, 26 cm). Two levers (5 cm wide) were inserted into the front wall, 7 cm above the floor, and 1 cm from each side. The levers were operated with a force of about 0.25 N. Just below each lever (2 cm) was an opening into which a 0.1-ml dipper could be raised. The dippers, when not raised, sat in a trough that held approximately 170 ml liquid. The trough that held ethanol had an aluminum cover in order to reduce evaporation. Experimental events were arranged and recorded with an IBM compatible personal computer that used MED-PC software (Tatham and Zurn 1989).

Responses at each lever were reinforced according to an independent variable-interval 5 s (VI 5 s) schedule. The intervals approximated a Poisson distribution and were based on the list derived by Fleshler and Hoffman (1962). Reinforcement consisted of 3 s access to a dipper. This was followed by a 1.5 s black-out period. Following the reinforcement and black-out periods, the timer that

had set up the reinforcer was restarted with a new, randomly selected, interval. Since the timers were independent, at any moment a reinforcer could set up at either or both levers. In addition, the subject had to stay at least 1 s at a side before a reinforcer would be delivered. (This contingency, called a "changeover delay," is a standard feature of concurrent schedule choice experiments, e.g., Findley 1958; Herrnstein 1970).

Procedure

Pre-experimental induction of ethanol consumption Prior to the results reported here, the subjects were induced to drink ethanol. One dipper served water, the other dipper served ethanol mixed with 10% sucrose solution (w/v). Ethanol concentration was varied from 5% to 20% (v/v). Each concentration was kept in effect until response rates were stable. The criterion was the absence of an increasing or decreasing trend for three consecutive sessions. Median consumption levels varied from 2.53 to 4.68 g/kg per half hour session. These amounts are higher than those obtained when ethanol was mixed with water (e.g., Samson 1987), but are similar to those in which ethanol was mixed with sucrose (Gilbert 1974) or in which ethanol was self-administered intragastrically (Amit and Stern 1969). This phase of the study lasted 71 sessions.

Following the 20% condition, ethanol concentration was returned to 10%, and a 2% sucrose solution was substituted for water in the second dipper. Sucrose concentration in the second dipper was then increased in 2% steps to 10%. Thus, at the end of the induction period one dipper provided 10% sucrose and the other dipper provided 10% sucrose plus 10% ethanol. This phase of the study lasted 30 sessions. Upon entering the first experimental condition, then, the subjects had consumed ethanol for 101 sessions.

Ethanol consumption measures Ethanol consumption was calculated in terms of the nominal number of reinforcers. Two observations indicate that the nominal values approximated the obtained values. First, the amount of ethanol beverage consumed during the session was estimated by measuring pre- and post-session trough volume. On average the amount of intake estimated in this way was 97% of the amount calculated from the nominal reinforcers. Second, in experiment 2, measured amounts of ethanol mix were placed in a dish in the experimental chamber. The rats drank from the dish prior to the session and also drank from the dippers during the session as in experiment 1. Across different pre-session servings of ethanol mix, total ethanol consumption remained approximately constant. This means that drinking from the dish and dipper had similar effects on satiation and that the amounts as measured by number of dipper operations were approximately the same as the amounts as measured into the dish. Ethanol amounts were expressed in terms of milliliters of absolute ethanol (ml) and body weight (g/kg). The gram measurements were based on the specific gravity of ethanol (0.79). For example, 1.0 g ethanol is equivalent to 1.27 ml ethanol.

Experiment 1: effect of pre-session access to sucrose on preference for ethanol

Introduction and procedure

Experiment 1 evaluated the effect of pre-session sucrose consumption on the reinforcing efficacy of sucrose and of ethanol mix. The sucrose was placed in a small dish (2.5 cm across). The dish was attached to a back corner of the experimental chamber by velcro strips. In the initial experimental condition, the dish held 5.0 ml sucrose. In subsequent conditions the amounts were 10.0 and 2.5 ml. Since dipper volume was 0.1 ml, pre-session meals were

equivalent to 50, 100, and 25 extra sucrose reinforcers. To acustom the rats to the dish, it was placed in the chamber for several sessions prior to the initial sucrose condition. The experimental session was 30 min long, but the timer was started by the subjects not the experimenter. The first two responses at either lever operated the associated dipper and started the session timer. This method was used so that the session would not begin until the

pre-session meal was consumed. Observation and the within-session pattern of responding indicated that this goal was met (as described in Results section). Each condition was kept in effect for a minimum of five sessions and a maximum of eight sessions, according to the rule that within these limits the condition would be changed if there was no monotonic trend in choice proportions for three consecutive sessions. Otherwise the procedure was as described in the General Methods section.

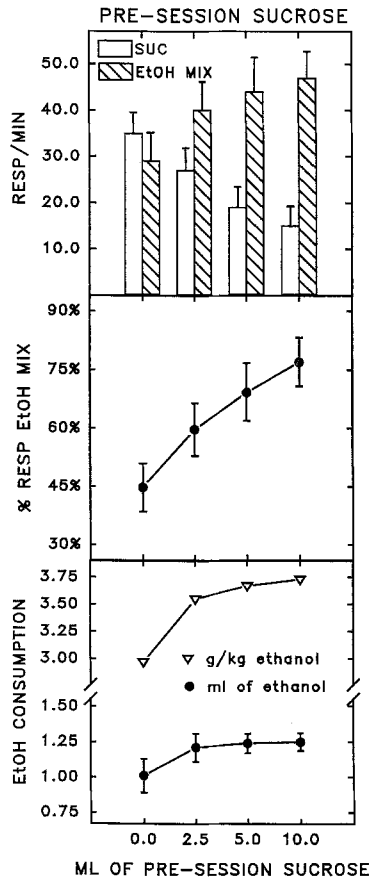


Fig. 1. The effect of pre-session sucrose on response rates, preference and ethanol consumption. The top panel shows response rates, the middle panel shows preference, and the bottom panel shows ethanol consumption. The data were averaged across subjects from the last three sessions of each condition. The error bars indicate one standard error of the mean

Results

The data displayed in Fig. 1 are based on the average response rates and number of ethanol-mix reinforcers. The data points represent group means, as calculated from the last three sessions of a condition, and the error bars indicate the between subject standard error of the mean. In subsequent figures displaying overall average response rates and ethanol consumption levels (e.g., Figs 3, 5, and 7), the data were collected in the same way.

The top panel of Fig. 1 shows that pre-session sucrose decreased responding maintained by sucrose [$F(3,15) = 13.2$; $P < 0.05$] but increased responding maintained by ethanol mix [$F(3,15) = 7.54$; $P < 0.05$]. Each subject showed this pattern. For instance, in the 18 possible comparisons between baseline and experimental conditions (6 subjects and 3 sucrose concentrations), response rates reinforced by ethanol mix were greater in 17 cases and response rates maintained by sucrose were lower in 16 cases. A repeated measures ANOVA was conducted on the differences in response rate (e.g., ethanol-mix response rate minus sucrose response rate). There was a significant linear trend between size of the pre-session sucrose meal and the size of the difference in response rates [$F(1,5) = 23.19$; $P < 0.05$].

The middle and bottom panels show average response proportions and ethanol consumption. Choice proportions for ethanol mix increased linearly as a function of increases in pre-session sucrose meals [$F(1,5) = 30.34$; $P < 0.05$]. Ethanol consumption increased during sessions that were preceded by sucrose meals. Each subject showed this pattern. In contrast, within-session sucrose consumption decreased. The decrements in the 2.5 and 5.0 ml conditions nearly offset the pre-session meal (1.5

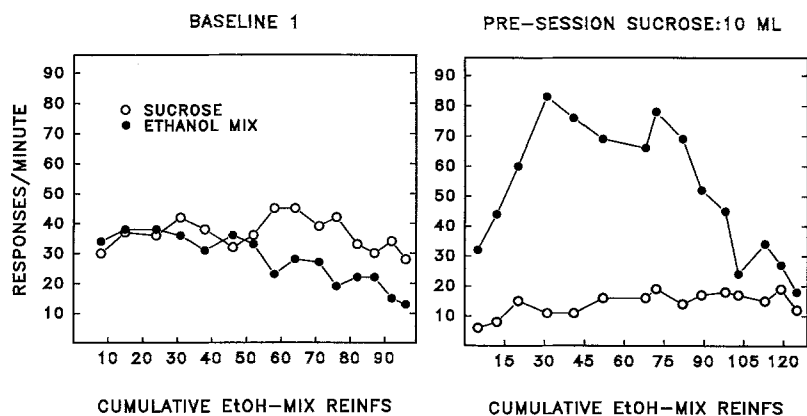


Fig. 2. Changes in within-session response rates as a function of cumulative ethanol-mix consumption. On the x-axis is the cumulative number of ethanol reinforcers obtained in consecutive 2-min samples. For example, in the first 2 min of the session the subjects averaged about 8 ethanol-mix reinforcers, whereas by the last 2 min of the session they had accumulated over 90 ethanol mixture reinforcers. On the y-axis is average response rate, as measured over consecutive 2-min periods. For example, the first data point gives the average response rate in the first 2 min of the session. The left panel shows the results from the last session in which there was no pre-session sucrose; the right panel shows the results from the last session in which there was a 10 ml pre-session serving of sucrose

and 4.0 ml, respectively). However, in the 10.0 ml condition, the average within-session decrement was about 5.2 ml so that in this condition, total sucrose consumption increased.

Figure 2 shows the within-session pattern of responding. The data were collected in consecutive 2-min bins. For example, the first filled circle shows that in the first 2 min of the session, the rats typically consumed about eight ethanol-mix reinforcers. On the y-axis is average response rate for each bin. Thus response rates are displayed as a function of cumulative ethanol consumption (and, indirectly, session time, since each data point represents a 2-min sample of behavior.) The data were drawn from the last session of a condition and averaged across subjects.

The left panel shows the within-session pattern of responding in the condition in which there was no pre-session access to sucrose (baseline). During the first half of the session, response rates at the two levers were about the same, usually between 30 and 40 responses/min. However, in the second half of the session, responding maintained by ethanol mix declined, falling to a level of about 12/min at the end of the session. In contrast, sucrose-maintained responding did not fall below 30/min until the last 2 min of the session.

The right panel of Fig. 2 shows the effects of the 10-ml pre-session sucrose meal on the within-session pattern of responding. Comparison with panel 1 (baseline) reveals the following points. First, at the start of the session, sucrose- and ethanol-mix-response rates were relatively low. In part, this occurred because the rats persisted in revisiting the dish even though they had emptied it of sucrose (informal observation). This tendency was more prominent at the beginning of the session and also more prominent in experiment 1. Second, pre-session sucrose meals delayed the decline in ethanol-mix response rates. For example, in baseline, ethanol-mix responding started to decline after about 50 ethanol-mix reinforcers, whereas, after 10 ml of pre-session sucrose, a similar decline did not start until about 70 ethanol-mix reinforcers.

As noted in the introduction to experiment 1, the subjects started the session timer by responding twice at either the left or right lever. The latencies for the first two responses increased from about 2 to 142 s as the pre-session meal increased from 0 ml (baseline) to 10 ml sucrose. These results agree with informal observation: the rats usually did not start lever pressing until they had emptied the dish.

Discussion and summary

The major findings were: pre-session meals of sucrose increased responding maintained by ethanol mix but decreased responding maintained by sucrose; ethanol-mix consumption increased, whereas within-session sucrose consumption decreased; and within-session ethanol-mix-maintained responding varied as a function of ethanol consumption, whereas within-session sucrose-maintained responding did not vary as a function of ethanol consumption. The results are consistent with one another

and indicate that the reinforcing consequences of ethanol mix and sucrose were different. Possible interpretations of these differences are reviewed in the General Discussion section of this report.

Although the failure of sucrose to substitute for ethanol mix (Heyman and Oldfather 1992) is consistent with the finding that pre-feeding did not attenuate the reinforcing efficacy of ethanol mix, the absence of substitutability does not provide a basis for the increase in ethanol-mix responding shown in Figs 1 and 2. Two additional principles are needed. First, pre-session sucrose consumption may have slowed the passage of ethanol from the stomach into the circulatory system. This in turn would delay feedback from ethanol's central effects, and, as noted in the General Discussion section, there is evidence that the level of ethanol consumption controlled responding maintained by ethanol mix. Second, it is also likely that reinforcer interactions, known as "contrast effects," led to the increase in response rate at the ethanol-mix lever. For example, as predicted by the matching law (Herrnstein 1970) and demonstrated by scores of studies (Williams 1988), a decrease in the magnitude or frequency of reinforcement at one alternative induces an increase in the response rate at the other alternative, even when the rate of reinforcement at the other alternative has not changed. Thus, the increase in response rates maintained by ethanol mix likely reflects the general principle (Herrnstein 1970) that response rate is a direct function of its reinforcement rate and an inverse function of concurrent reinforcement rates.

Experiment 2: effects of pre-session ethanol mix on within-session preference for ethanol mix

Introduction

The finding that pre-session sucrose increased preference for ethanol mix suggests the converse relationship: that pre-session ethanol mix should increase preference for sucrose. This was tested by providing the rats with different amounts of ethanol mix at the start of the session.

Procedure

The rats used in experiment 1 were returned to baseline (an empty sucrose dish). Stable preferences were established, and then the dish was filled with ethanol mix. The pre-session portions, in order, were 5.0, 10.0, and 2.5 ml. This was equivalent to 50, 100, and 25 ethanol-mix reinforcers. Each condition was maintained for eight sessions. Otherwise the procedure was as described in the General Methods section.

Results

The top panel of Fig. 3 shows that pre-session access to ethanol mix decreased responding maintained by ethanol mix [$F(3,15) = 13.8$; $P < 0.05$], but increased responding

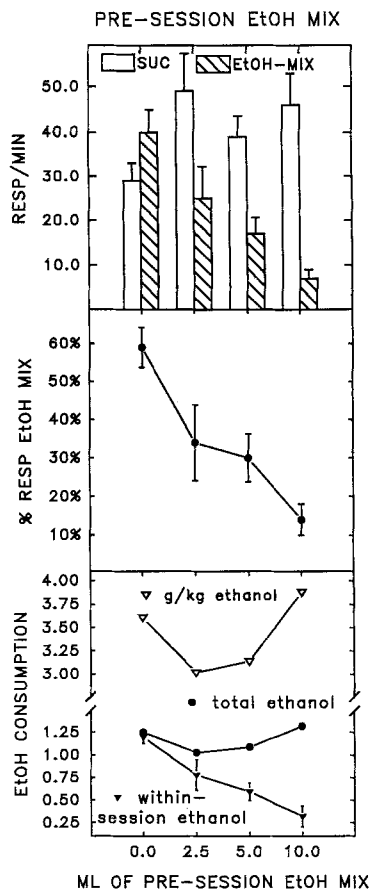


Fig. 3. The effect of pre-session ethanol mix on response rates, preference and ethanol consumption. The data were averaged across subjects from the last three sessions of each condition, as in Fig. 1. Error bars indicate one standard error of the mean

maintained by sucrose [$F(3,15)=5.4$; $P<0.05$]. Differences between the two rates (ethanol-mix response rate minus sucrose response rate) increased linearly with the size of the pre-session ethanol-mix-servings [$F(1,5)=126.66$; $P<0.05$]. Each subject showed this pattern. For instance, in 18 of 18 instances the difference between ethanol-mix- and sucrose-reinforced response rates increased relative to baseline.

The middle and bottom panels show change in relative response rates and ethanol consumption. Preference for ethanol mix decreased linearly with the size of the

pre-session meal [$F(1,5)=32.8$; $P<0.05$]. Within-session ethanol consumption also decreased. However, total ethanol consumption, counting both the pre-session- and within-session serving, remained approximately constant. For example, across the four conditions of this study, average total ethanol intake varied between 1.03 and 1.31 ml. This implies that the magnitude of the within-session decrease in ethanol consumption was about equal to the size of the pre-session serving.

Figure 4 shows the within-session pattern of responding in baseline and the 5 ml ethanol-mix condition. As in experiment 1, sucrose-reinforced responding did not vary as a function of ethanol consumption. In contrast, responding maintained by ethanol mix varied as a function of both pre-session and within-session ethanol consumption. For instance, in the baseline session, ethanol-mix-maintained responding began to decline after 45 ethanol-mix reinforcers had been delivered, whereas after a 5 ml pre-session serving of ethanol mix, this decline began after 15 ethanol-mix reinforcers had been delivered. The within-session patterns of responding in the 2.5 ml and 10.0 ml conditions were similar: sucrose-maintained responding remained relatively constant, whereas responding reinforced by ethanol mix declined as a function of ethanol-mix consumption.

Baseline 1, which preceded experiment 1, and baseline 2, which followed experiment 1, were procedurally identical. However, in baseline 2 preference for the ethanol mix was markedly greater in three subjects, and average preference for ethanol mix increased from about 45% to 59%. Following experiment 2, average preference for ethanol mix did not fall below 50%.

Discussion

Pre-session servings of ethanol mix decreased responding maintained by ethanol mix but not responding maintained by sucrose. However, within-session decreases in consumption of ethanol mix were roughly equal to pre-session serving sizes. Thus, overall ethanol consumption remained approximately constant. This means that the changes in response rate and preference were a simple function of the amount of ethanol consumed.

However, if overall ethanol-mix consumption did not vary much, why did responding maintained by sucrose

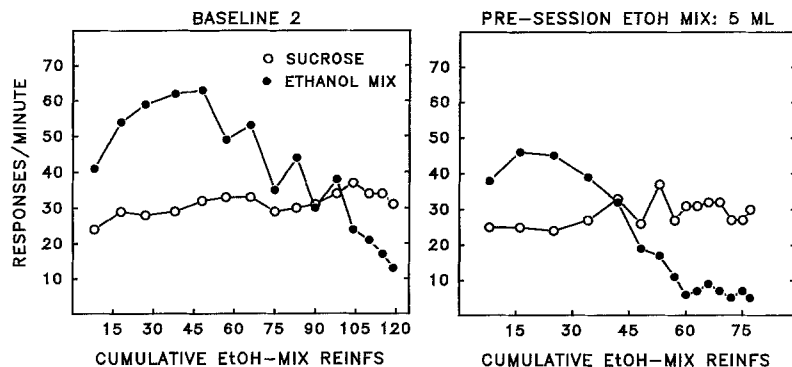


Fig. 4. Within-session response rates as a function of cumulative ethanol-mix consumption. The data were collected and plotted as in Fig. 2

increase? The most likely account is that the increase in sucrose responding was a contrast effect. For example, according to the principle that the efficacy of a reinforcer is an inverse function of concurrent reinforcers (the matching law: Herrnstein 1970), a decrease in the reinforcing efficacy of ethanol mix would bring about an increase in the reinforcing efficacy of sucrose. It also should be noted that the increases in response rate at the sucrose lever resulted in no more than a 0.3 g increase in sucrose consumption.

Experiment 3: effects of increases in body weight on preference for ethanol mixture

Introduction

Previous research shows that responding maintained by foods and by saccharin varied inversely with changes in body weight (e.g., Sheffield and Roby 1950; Kimble 1960; McSweeney 1975; Gill and Nielson 1979; Snyderman 1983). Similarly, increases in body weight also decreased ethanol consumption and the reinforcing efficacy of ethanol, as measured by preference (e.g., Meisch and Thompson 1973, 1974; Roehrs and Samson 1982). Moreover, the inverse relationship between body weight and ethanol preference was found in studies with selectively bred, ethanol preferring (P) rats (Waller et al. 1982) and with rats introduced to ethanol with the procedures developed by Samson (Pfeffer and Samson 1985). However, in experiment 1, pre-session feeding decreased sucrose consumption without decreasing ethanol consumption. This suggests that in the procedure used in experiment 1, ethanol consumption may be relatively independent of factors that influence the reinforcing efficacy of food. Experiment 3 tests this prediction in terms of changes in body weight.

Procedure

Body weight was manipulated by increasing the post-session meal (chow). For instance, the rats were given 3–6 chow pellets rather than the standard 1.5 to 3 pellets as in experiments 1 and 2. Weight was incremented in 5% and 10% steps, and each new target weight was kept in effect for 6–15 sessions, depending on whether choice proportions were stable. (As in the initial, ethanol induction period, stability was defined as the absence of a monotonic trend in choice proportions for three consecutive sessions.) Throughout, weight percentages were calculated in terms of the body weight just prior to the start of the experiment (about 292–314 g). Otherwise the procedure was as described in the General Methods section.

Results

The top panel of Fig. 5 shows that increases in body weight tended to decrease responding maintained by sucrose but did not have consistent effects on responding

maintained by ethanol mix. The overall (omnibus) F for change in sucrose responding was not significant at the 0.05 level [$F(5,25)=2.04 < 0.11$], but a higher order polynomial contrast to evaluate the more focused hypothesis of whether sucrose responding decreased as body weight increased was significant [e.g., order 4: $F(1,5)=7.5$; $P < 0.05$]. Differences between the two response rates increased from -12 to $+16$ responses/min as body weight increased (ethanol-mix response rate minus sucrose response rate), but again the overall analysis of variance was not significant at the 0.05 level [$F(5,25)=1.73$; $P < 0.17$]. In the 30 possible comparisons (6 subjects and 5 body weights greater than 85% of the initial free-feeding value), response rates maintained by ethanol mix were greater in 21 cases and response rates maintained by sucrose were lower in 22 cases.

The middle panel shows average relative response rates. For four of the six subjects, preference for ethanol mix increased linearly as a function of body weight [$F(1,3)=15.6$; $P < 0.05$]. However, for two subjects (rats 122 and 125) preference for ethanol mix was highest during an intermediate body weight and lowest at the highest body weight. Consequently, the overall F for changes in preference for the group was not significant at the 0.05 level [$F(5,25)=1.6$; $P < 0.21$].

The bottom panel shows that ethanol consumption, as measured in milliliters, remained relatively constant.

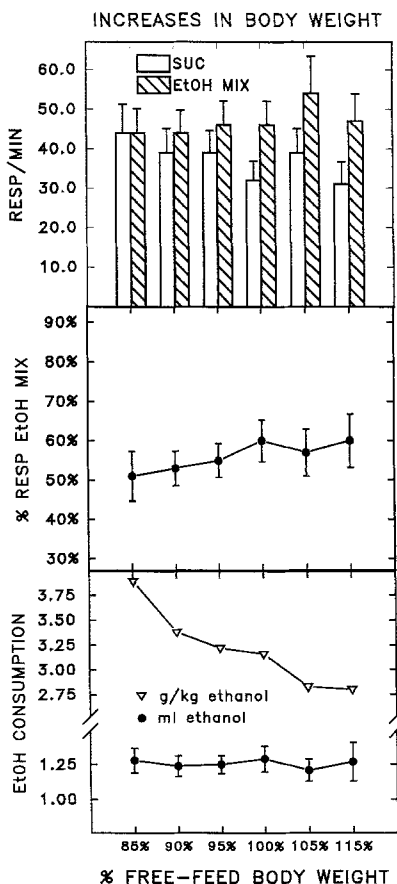


Fig. 5. The effect of changes in body weight on response rates, preference and ethanol consumption. The data were collected and plotted as in Figs 1 and 3

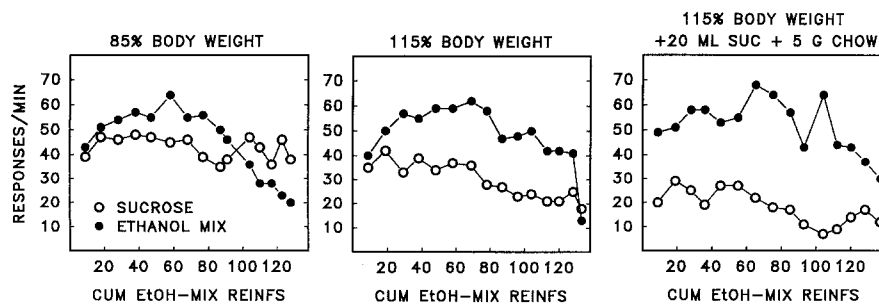


Fig. 6. Within-session response rate as a function of cumulative ethanol-mix consumption in experiments 3 and 4. The data were collected and plotted as in Figs 2 and 4

For example, the difference between the lowest and highest average consumption level was not more than 0.02 ml. Thus, the decrease in ethanol consumption as measured in g/kg simply reflects the increase in body weight.

Figure 6 shows that increases in body weight had opposite effects on the within-session patterns of responding maintained by ethanol mix and by sucrose. Responding reinforced by sucrose reached a peak of about 40 responses/min near the start of the session, but then steadily declined, reaching a level of about 20/min at the end of the session. In contrast, increases in body weight delayed the decline in responding maintained by ethanol mix. For instance, at the 115% body weight, ethanol-mix response rates did not fall below 40 responses/min until more than 120 ethanol-mix reinforcers had been consumed.

Discussion

In previous studies, increases in body weight decreased ethanol consumption and responding maintained by ethanol (e.g., Meisch and Thompson 1973, 1974; Waller et al. 1982; Pfeffer and Samson 1985). However, the finding that sucrose was a relatively poor substitute for ethanol mix (Heyman and Oldfather 1992) suggested that, up to some limit, factors that decreased the reinforcing efficacy of sucrose would not decrease the reinforcing efficacy of ethanol mix. The results displayed in Fig. 5 support this hypothesis. However, unlike experiments 1 and 2, there were individual differences in the relationship between the independent variables and preference. Four subjects showed a linear increase in preference for ethanol mix as body weight increased, but two did not. For these two subjects, the lowest ethanol-mix response rates occurred at the highest body weight. This suggests that further increases in feeding might decrease responding maintained by ethanol mix in all subjects. Experiment 4 tests this idea.

Experiment 4: effects of pre-feeding on ethanol-mix preference in non-food deprived rats

Introduction and procedure

In experiments 1 and 3, manipulations that decreased sucrose-reinforced response rates did not on average decrease ethanol-mix-reinforced response rates. However,

since ethanol mix provides calories, it seems reasonable to suppose that at some point manipulations that decreased the reinforcing efficacy of sucrose would also attenuate the reinforcing efficacy of ethanol mix. In experiment 4 this limit was assessed by combining the manipulations employed in experiments 1 and 3. The rats were maintained at the final target weight of experiment 3, 115% initial free-feeding values, and were pre-fed with both sucrose and chow. In the final two conditions of this experiment, pre-session meals were relatively large, e.g., 20 ml sucrose plus 5 and 10 g chow, and the rats gained weight, reaching 125% of their initial free-feeding values. Consequently, post-session meals were reduced to a fraction of a chow bit. Thus, in this phase of the study, the rats received nearly all of their food as well as all of their ethanol in the experimental session. Pre-session chow and sucrose were placed in a dish, as in experiment 1. Each feeding condition was kept in effect for 6–20 sessions, as determined by the stability criterion (no monotonic trend in choice proportions for three consecutive sessions). Otherwise the procedure was as described in General Methods.

Results

Extra access to chow increased body weights above the 115% target values. For instance, when the pre-session meal consisted of 20 ml sucrose plus 10 g of chow, the rats gained 16 g in 11 days, reaching body weights that were 47% greater than the weights in experiments 1 and 2 and 25% greater than their initial free-feeding weights. Thus, in the conditions with chow pre-feeding, there were increases in body weight as well as increases in pre-session meal size.

The top panel of Fig. 7 shows that when the rats were at 115–125% of their initial free-feeding weight, pre-session meals decreased responding maintained by sucrose [$F(4,20)=13.96$; $P<0.05$]. In contrast, pre-feeding did not produce consistent changes in responding maintained by ethanol mix [$F(4,20)=2.47$; $P<0.08$]. For instance, the smallest pre-session meal was followed by a significant increase in ethanol-mix responding [$t(5)=(2.51)$; $P<0.05$], whereas the largest pre-session meal was followed by a significant decrease in ethanol-mix responding [$t(5)=3.23$]; $P<0.05$]. However, the differences in response rate (ethanol mix minus sucrose) increased linearly as a function of pre-session meal size [$F(1,5)=9.35$; $P<0.05$], as in experiment 1. Similarly, choice proportions for ethanol mix increased linearly

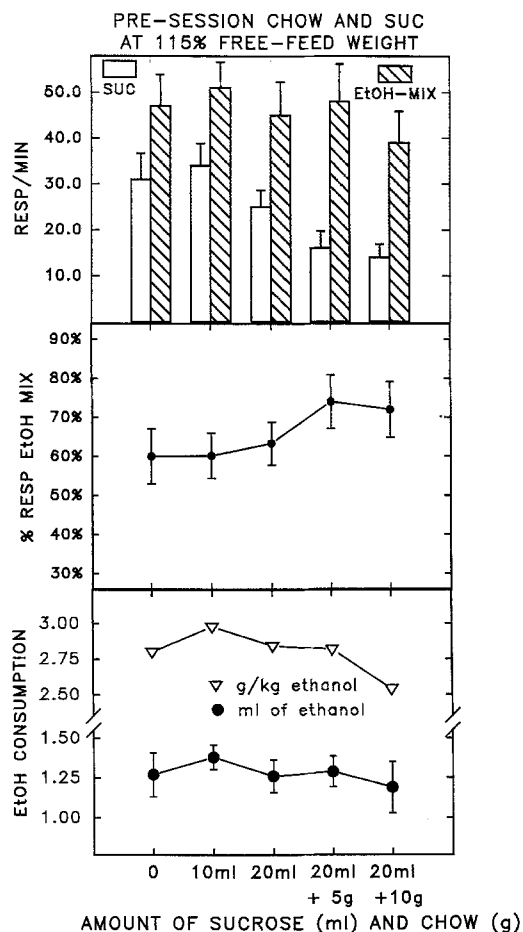


Fig. 7. The effect of pre-session feeding at 115% body weight on response rate, preference and ethanol consumption. The data were collected and plotted as in Figs 1, 3, and 5

(middle panel of Fig. 7). And, as in experiments 2 and 3, ethanol consumption (bottom panel of Fig. 7) remained relatively constant at about 1.25 ml/session.

The third panel of Fig. 6 shows the within-session patterns of responding when the rats were at 115% body weight and pre-fed with both sucrose and chow. Comparison with the 85% and 115% graphs (left and middle panels) shows that the primary effect of the pre-session meal was to decrease responding maintained by sucrose. For instance, responding reinforced by sucrose began to decline after about 20 ethanol-mix reinforcers (4 min into the session), whereas responding maintained by ethanol mix did not fall below 40 responses/min until more than 100 ethanol-mix reinforcers.

Pre-session meals of sucrose and chow also increased the latency to the initiation of lever pressing. For example, when the pre-session meal was 10 ml sucrose, the latency to start lever pressing was on average 87 s, but with the largest meal, 20 ml sucrose plus 10 g chow, the latency was on average 1283 s.

Discussion

The results of experiment 4 replicate and extend those of experiment 1. First, pre-session feeding increased prefer-

ence for ethanol mix, even though the subjects were at 115% of their initial free-feeding body weights. Second, pre-session chow produced results that were similar to pre-session sucrose. This suggests that a variety of pre-session meals would decrease responding maintained by sucrose without also decreasing responding maintained by ethanol mix. Third, the two subjects that showed a decrease in preference for ethanol mix in the last condition of experiment 3 (rats 122 and 125) did not show further decreases in preference. Instead, pre-session meals increased preference for ethanol mix in rats 122 and 125, as it did in the other subjects.

However, the final condition of experiment 4 may mark the beginning of a boundary condition. When meal size reached 10 g chow plus 20 ml sucrose, ethanol-mix response rates decreased in every rat. This did not, however, have much effect on ethanol consumption, because, despite the decreases, responding remained relatively high (about 39/min on average).

Experiments 5 and 6: control for side bias and pre-feeding

Introduction and procedure

All the subjects showed similar changes in preference in experiments 1, 2, and 4. However, in experiment 3, two rats showed a bitonic relationship between changes in body weight and preference for ethanol mix. One possible explanation is that during experiment 3 side preferences became stronger. For example, a side preference for the sucrose dipper would attenuate the effect of manipulations that increased preference for the ethanol mix. To test this possibility, the troughs were simply switched so that the dipper that had served ethanol mix now served sucrose, and conversely for the dipper that had served sucrose. For all but one subject (rat 121) this meant moving the ethanol mixture from the right to the left trough. Otherwise the conditions were kept as in the last phase of experiment 4: the rats were pre-fed 20 ml sucrose and 10 g chow. These conditions were in effect for eight sessions, as determined by the stability criterion (no monotonic trend in choice proportions for three sessions).

In experiment 6, ethanol was removed from the experiment, and the effect of pre-session sucrose on preference for two identical sucrose solutions was evaluated. First, stable preferences for the two 10% sucrose solutions were established (12 sessions), and then the subjects were pre-fed 5 ml 10% sucrose, as in experiment 1 (6 sessions). Thus, this manipulation simply controls for the effect of pre-feeding on preference. For example, would pre-feeding increase or decrease side biases?

Results

Switching sides so that ethanol mix was on the side that had served sucrose, increased absolute response rates maintained by ethanol mix to about the highest level observed in experiment 3 (on average 51 responses/min) and decreased response rates maintained by sucrose to

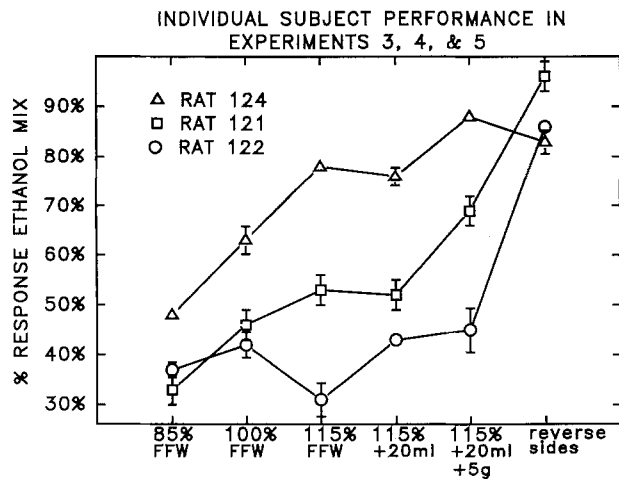


Fig. 8. Preference for ethanol mixture in three subjects as a function of body weight (experiment 3), pre-feeding (experiment 4) and side (experiment 5). The data were averaged from the last three sessions of each condition. The error bars give the standard error between sessions. In contrast, the error bars in the previous graphs included between subject variation, as well as between session variation

about 8 responses/min. The average increase in preference for ethanol mix was about 14%, and three subjects moved to nearly exclusive preference (95% or greater). The two rats (122 and 125) that showed a bitonic relationship between body weight and preference for ethanol mix in experiment 3 were most affected by the location of the two reinforcers. For example, Fig. 8 shows that switching sides, nearly doubled ethanol-mix preference in rat 122. Figure 8 also shows the results for two subjects (rats 121 and 124) whose performance was most similar to the group average values. For these two rats, increases in body weight and pre-session meals consistently increased preference for ethanol mix. Since Fig. 8 shows individual subjects, the error bars do not include between subject variation. The average standard error was about 2% of the mean. Thus most of the variability within a condition was due to individual differences rather than to within subject differences (e.g., session-to-session variability).

In experiment 6 both dippers served a 10% sucrose solution (ethanol was not available). Once stability was attained (12 sessions), the rats were pre-fed with 5 ml sucrose in the dish used in previous conditions. In the absence of pre-feeding, preference for the side that had served ethanol (before the reversal) averaged 45%. With pre-feeding the average preference was 43%, and the number of subjects showing increases and decreases was the same.

Discussion

Four of six subjects showed a greater preference for ethanol mix when it was switched to the side that had served sucrose. The increases appeared in the first session that sucrose and ethanol mix were switched and were largest for the two subjects that showed a bitonic relationship between body weight and preference in experiment 3. This suggests that these two rats may have developed a side bias during experiment 3.

In the last condition of experiment 4, a pre-session meal of 20 ml sucrose and 10 g of chow decreased response rates reinforced by ethanol mix in each subject, suggesting a boundary condition. However, these feeding conditions were retained in experiment 5 and ethanol-mix response rate increased in four subjects when dipper contents were reversed. Thus the point at which increased access to food will consistently reduce responding maintained by ethanol mix remains unclear.

In experiment 6, ethanol was removed and 10% sucrose was available in both dippers. There was a slight bias for the side that normally did not serve ethanol, and this was unaltered by pre-feeding. Thus, pre-feeding had little or no effect on preference when ethanol was not available.

General discussion

The experimental manipulations differentially changed rates of responding depending on whether the reinforcer was ethanol mix or sucrose. In the experiments in which food or ethanol mix was served just prior to the session, changes in response rate were a simple linear function of the magnitude of the pre-session manipulation. Increases in body weight also tended to differentially change response rates reinforced by ethanol mix and by sucrose. In four subjects, preference (relative response rate) for ethanol mix increased linearly with body weight, and in the other two subjects, the relationship between preference and body weight was bitonic. Thus, the results were qualitatively consistent with one another, and in most instances, a simple linear model described their quantitative features.

Pre-session meals (e.g., experiments 1 and 4) and increases in body weight (experiment 3) decreased responding maintained by sucrose, but typically did not decrease responding maintained by ethanol mix. The logical implication is that ethanol mix provided reinforcing consequences that sucrose did not provide. Previous research suggests several possible explanations for the capacity of ethanol mix to function as an effective reinforcer under conditions in which the reinforcing efficacy of sucrose decreased.

There is evidence that in rats the reinforcing effects of ethanol are a function of its caloric consequences (Lester and Freed 1973; Dole 1986). However, in the studies reported here, conditions which reliably decreased the reinforcing efficacy of food (de Villiers and Herrnstein 1976; Snyderman 1983), increased preference for ethanol mix, and, conversely, factors which decreased the reinforcing efficacy of ethanol mix failed to decrease the reinforcing efficacy of sucrose. These findings do not support the view that preference for ethanol mix was based on its caloric consequences.

Possibly the rats preferred ethanol mix because of its taste. For example, even though 10% ethanol is aversive in rats (e.g., Richter and Campbell 1940; Kahn and Stellar 1960; Kiefer et al. 1990), mixing ethanol with sucrose might yield a uniquely palatable taste. For example, hu-

mans and monkeys develop preferences for tastes that are initially aversive, such as for chili peppers (e.g., Rozin and Kennel 1983). However, there was no evidence that the increase in preference for ethanol mix was based on its taste. First, at the end of the induction period, prior to the start of Experiment 1, four of the six rats preferred sucrose to ethanol mix. That is, there was an initial bias, albeit slight, toward sucrose not toward ethanol mix. Second, in previous studies preferences based on flavor decreased as deprivation decreased. For instance in experiments with rats, preference for saccharin decreased as feeding increased (e.g., Sheffield and Roby 1950). In contrast, in experiments 1, 3, and 4 preference for ethanol mix increased as feeding increased.

The simplest and most comprehensive account of the results is that the reinforcing efficacy of ethanol mix was a function of its pharmacological effects. First, as has been emphasized, pre-session feeding and increases in body weight, typically did not decrease responding maintained by ethanol mix. This can be explained in terms of substitutability and pharmacological effects. If sucrose and chow are poor substitutes for ethanol's pharmacological effects then there should be conditions under which increased access to either of these foods will not decrease the reinforcing efficacy of ethanol mix. By analogy, in a variety of settings increased access to water did not decrease the reinforcing efficacy of food (e.g., Rachlin et al. 1976; Hursh 1978; Green and Rachlin 1991).

Second, ethanol's pharmacological effects provide a basis for the within-session patterns of responding. As shown in Figs 2, 4, and 6, responding reinforced by ethanol mix declined in an orderly way as a function of ethanol consumption. It is not likely that this was due to food satiation, since responding maintained by sucrose continued unabated to the end of the session. However, the pharmacological effects of ethanol can be aversive. For example, rats learn to avoid flavors that have been paired with intra-gastric (Berman and Cannon 1974) or intraperitoneal (Davies and Parker 1990; Stewart et al. 1991) injections of ethanol. Thus the reinforcing efficacy of ethanol mix may have declined because ethanol's pharmacological effects became aversive. More generally, the view that ethanol's pharmacological effects controlled behavior explains (1) the failure of sucrose to substitute for ethanol mix (e.g., Heyman and Oldfather 1992), (2) the failure of extra-access to food to attenuate the reinforcing efficacy of ethanol mix (experiments 1, 3, 4, and 5), and (3) the within-session decline in ethanol-mix reinforcing efficacy (Figs 2, 4, and 6).

In contrast to the results described in this report, rats have not maintained constant ethanol consumption levels in previous studies in which body weight was varied or in which sucrose was introduced as the alternative reinforcer (e.g., Meisch and Thompson 1973, 1974; Roehrs and Samson 1982; Waller et al. 1982; Schwarz-Stevens et al. 1991). Two factors that may have contributed to the different results are as follows.

First, prior to the start of experiment 1, the rats had a 101 session history of drinking ethanol mix. During this period, intake varied between about 2.5 and 4.5 g/kg per 30 min. In contrast, in other studies, rats did not drink as

much, as measured by rate, and there was not as long a pre-experimental drinking period.

Second, since the experiment provided two sources of calories, it was logically possible for conditions to be arranged such that ethanol consumption was independent of feeding conditions. To see that this is the case, consider the hypothesis that ethanol-mix consumption was controlled by two factors, its calories and its pharmacological effects, and that pharmacological "satiation" occurred first. Under these conditions, the subjects would first satiate on ethanol mix and then, depending on such factors as body weight and deprivation, continue to consume sucrose (see, e.g., Figs 2, and 4). Thus, ethanol-mix consumption would remain relatively constant, independent of changes in the availability of extra food (e.g., Figs 1 and 5). However, if there were not a second source of palatable calories, then, by this theory, ethanol consumption would vary as a function of both caloric and pharmacological consequences. The data support the two factor hypothesis. In experiment 3 of this report, increases in body weight did not decrease responding maintained by ethanol mix, whereas in studies in which ethanol was the only available food source, increases in body weight decreased ethanol consumption or responding maintained by ethanol (Roehrs and Samson 1982; Waller et al. 1982; Pfeffer and Samson 1985). Also, note that this theory predicts signs of caloric influence if conditions are arranged so that caloric satiation occurred at about the same time or sooner than pharmacological satiation. For example, if a large pre-session meal caused caloric satiation early in the session then ethanol consumption would vary as a function of feeding conditions (and perhaps, also, pharmacological consequences). As evidence, in experiment 4, the largest meal pre-session meal, 20 ml sucrose plus 10 g chow, decreased ethanol-mix-maintained responding.

In previous studies with rats and other animals, qualitatively different reinforcers were usually relatively substitutable for one another. For instance in experiments with rats, tom collins mix substituted for root beer (Rachlin et al. 1976), brain stimulation reward substituted for food and for water (Green and Rachlin 1991), and sucrose substituted for chow almost as well as did chow itself (Lea and Roper 1977). However, in contrast to these results, sucrose was a relatively poor substitute for ethanol mix (Heyman and Oldfather 1992; Heyman 1993). The results from experiments 1-5 were consistent with this finding. The simplest explanation of the three studies is that ethanol's reinforcing properties depended on its pharmacological effects and thus sucrose was a poor substitute. Further study of this hypothesis will increase our understanding of the determinants of ethanol's capacity to reinforce behavior in rats and probably other animals, and, more generally, research on preference for ethanol mix relative to sucrose will provide a better understanding of the determinants of inelastic preferences and substitutability between reinforcers.

Acknowledgements. I would like to thank Kris Kirby and Phil Rodkin for their help with the statistical analyses, Dick Meisch and and Mitchell Macenski for their comments on an earlier draft of this

paper. This research was funded by grant RO3-AA08731 from the National Institute of Alcohol Abuse and Alcoholism.

References

- Amit Z, Stern MH (1969) Alcohol ingestion without oropharyngeal sensations. *Psychon Sci* 15:162–163
- Baumol WJ, Blinder AS (1988) *Economics, principles and policy, microeconomics*, 4th edn. Harcourt Brace Jovanovich, San Diego
- Berman R, Cannon, D (1974) The effect of prior ethanol experience on ethanol-induced saccharin aversions. *Pharmacol Biochem Behav* 12:1041–1044
- Davies BT, Parker LA (1990) Novel versus familiar ethanol: a comparison of aversive and rewarding properties. *Alcohol* 7:523–529
- de Villiers PA, Herrnstein RJ (1976) Toward a law of response strength. *Psychol Bull* 83:1131–1153
- Dole VP (1986) On the relevance of animal models to alcoholism in humans. *Alcohol Clin Exp Res* 10:361–363
- Findley JD (1958) Preference and switching under concurrent scheduling. *J Exp Anal Behav* 1:123–144
- Fleshler M, Hoffman HS (1962) A progression for generating variable-interval schedules. *J Exp Anal Behav* 5:529–530
- Gilbert RM (1974) Effects of food deprivation and fluid sweetening on alcohol consumption by rats. *Q J Stud Alcohol* 35:42–47
- Gill JH, Nielson HC (1979) A specific arousal effect from barpressing on nonspecific arousal in rats. *Physiol Psychol* 7:447–450
- Green L, Rachlin H (1991). Economic substitutability of electrical brain stimulation, food, and water. *J Exp Anal Behav* 55:133–143
- Herrnstein RJ (1970) On the law of effect. *J Exp Anal Behav* 13:243–266
- Heyman GM (1993) Response requirement increases fail to decrease preference for ethanol beverage in rats [Abstract] *Alcohol Clin Exp Res* 17:480
- Heyman GM, Oldfather CM (1992) Inelastic preference for ethanol in rats: an analysis of ethanol's reinforcing effects. *Psychol Sci* 3:122–130
- Hursh S (1978) The economics of daily consumption controlling food- and water-reinforced behavior. *J Exp Anal Behav* 29:475–491
- Kahn M, Stellar E (1960) Alcohol preference in normal and anosmic rats. *J Comp Physiol Psychol* 53:571–575
- Kiefer SW, Bice PJ, Orr MR, Dopp JM (1990) Similarity of taste reactivity responses to alcohol and sucrose mixtures in rats. *Alcohol* 7:115–120
- Kimble GA (1961) *Hilgard and Marquis' conditioning and learning*, 2nd edn. Appleton-Century-Crofts, New York
- Lea S, Roper T (1977) Demand for food on fixed-ratio schedules as a function of the quality of concurrently available reinforcement. *J Exp Anal Behav* 27:371–380
- Lester D, Freed EX (1973) Criteria for an animal model of alcoholism. *Pharmacol Biochem Behav* 1:103–107
- Mansfield E (1982) *Microeconomics, theory and applications*, 4th edn. W.W. Norton, New York
- McSweeney FK (1975) Concurrent schedule responding as a function of body weight. *Anim Learn Behav* 3:264–270
- Meisch R, Thompson T (1973) Ethanol as a reinforcer: effects of fixed ratio size and food deprivation. *Psychopharmacology* 28:171–183
- Meisch R, Thompson T (1974) Ethanol intake as a function of concentration during food deprivation and satiation. *Pharmacol Biochem Behav* 2:589–596
- Pfeffer AO, Samson HH (1985) Oral ethanol reinforcement: Interactive effects of amphetamine, pimozide, and food-restriction. *Alcohol Drug Res* 6:37–48
- Rachlin HC, Green L, Kagel JH, Battalio RC (1976) Economic demand theory and psychological studies of choice. In: Bower G (ed) *The psychology of learning and motivation*, vol 10. Academic Press, New York, pp 129–154
- Richter CP, Campbell KH (1940) Alcohol taste thresholds and concentrations of solutions preferred by rats *Science* 91:507–508
- Roehrs TA, Samson HH (1982) Relative responding on concurrent schedules: indexing ethanol's reinforcing efficacy. *Pharmacol Biochem Behav* 15:539–544
- Rozin P, Kennel K (1983) Acquired preferences of piquant foods by chimpanzees. *Appetite* 4:69–77
- Samson HH (1987) Initiation of ethanol-maintained behavior: a comparison of animal models and their implication to human drinking. In: Thompson T, Dews P, Barrett J (eds) *Advances in behavioral pharmacology*, vol. 6. Erlbaum, Hillsdale
- Sheffield FD, Roby TB (1950) Reward value of a nonnutritive sweet taste. *J Comp Physiol Psychol* 43:471–481
- Schwarz-Stevens K, Samson HH, Tolliver GA, Lumeng L, Li T-K (1991) The effects of ethanol initiation procedures on ethanol reinforced behavior in the alcohol-preferring rat. *Alcohol Clin Exp Res* 15:277–285
- Snyderman M (1983) Body weight and response strength. *Behav Anal Letts* 3:255–265
- Stewart RB, McBride WJ, Lumeng L, Li T-K (1991) Chronic alcohol consumption in alcohol preferring P rats attenuates subsequent taste aversion produced by ethanol injections. *Psychopharmacology* 105:530–534
- Tatham TA, Zurn KR (1989) The MED-PC experimental apparatus programming system. *Behav Res Methods, Instr Comp* 21:294–302
- Waller MB, McBride WJ, Lumeng L, Li T-K (1982) Induction of dependence on ethanol by free-choice drinking in alcohol preferring rats. *Pharmacol Biochem Behav* 16:501–507
- Williams BA (1988) Reinforcement, choice, and response strength. In Atkinson RC, Herrnstein RJ, Lindzey G, Luce RD (eds) *Stevens' handbook of experimental psychology*, 2nd edn. Wiley, New York, pp 167–244