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RELATIVE REINFORCING EFFECTS OF DIFFERENT ORAL ETHANOL DOSES IN RHESUS MONKEYS

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The relative reinforcing effects of different doses of orally delivered ethanol were evaluated. Mouth-contact responding by rhesus monkeys was measured under concurrent fixed-ratio fixed-ratio schedules of liquid delivery (0.67 ml/delivery) from each of two spouts during daily 3-hr sessions. Experiment 1 examined persistence of responding with ethanol (2%, 8%, and 32% wt/vol) and water available. When fixed-ratio values from 8 to 128 were tested, the number of ethanol deliveries obtained per session decreased as the response requirement increased. The decrease in deliveries was less at higher than at lower ethanol concentrations, however. Experiment 2 examined choice between two ethanol concentrations under concurrent fixed-ratio 16 schedules (4% vs. 8%, 4% vs. 16%, 8% vs. 16%, 2% vs. 8%, 2% vs. 32%, 8% vs. 32%). Higher concentrations (16%, 32%) generally maintained more responding than concurrently available concentrations of 8% or less. An exception was the observation of a preference for 8% over 32% ethanol. When the fixed-ratio value was increased, however, the relative preference for these two doses was reversed so that 32% ethanol maintained more responding than 8% ethanol. Thus, the direction of the preference depended on the size of the response requirement. These results indicate that the reinforcing effects of ethanol increase with dose.

Key words: drug self-administration, oral route, alcohol, reinforcer magnitude, concurrent fixed-ratio schedules, mouth-contact responses, rhesus monkeys

In drug self-administration studies, when response rate is the dependent variable and the amount of drug available per delivery is the independent variable, a bitonic inverted-U-shaped dose–response curve typically is generated (Meisch & Lemaire, 1993; Woolverton & Nader, 1990; Young & Herling, 1986). At least this is the case under simple reinforcement schedules such as fixed-ratio (FR) schedules. For example, in a study by Meisch and Thompson (1974), oral ethanol-reinforced lever pressing by rats under an FR 1 schedule increased as the ethanol dose per dipper delivery (i.e., the ethanol concentration) was raised in steps from 2% to 8% wt/vol. Thereafter, responding decreased as a function of further increases in the ethanol dose.

A possible explanation for decreases in drug deliveries at high doses is that direct drug effects decrease response rates. Results from several studies show, however, that such an explanation is insufficient to account for the general finding of inverted-U-shaped dose–response functions (Bickel, Marsch, & Carroll, 2000). In one study, for example, a saccharin solution was concurrently available with phencyclidine under identical FR schedules (Carroll, 1985). Phencyclidine-reinforced responding was an inverted-U-shaped function of dose. Responding maintained by saccharin, however, continued after responding maintained by phencyclidine had ceased. These results were interpreted as showing that discontinuation of responding on the spout delivering phencyclidine was likely due to drug satiation and not to impairment of behavior or satiation caused by liquid intake (for a further discussion of direct drug effects, see Bickel et al., 2000).

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It is often assumed that the doses at the peak of this inverted-U-shaped curve (e.g., 8% wt/vol ethanol) are the most reinforcing, and that higher doses on the descending limb of the curve (e.g., 32% wt/vol ethanol) are less reinforcing or even aversive (Katz, 1989). There is strong evidence from studies with other drugs, however, that higher drug doses are more reinforcing than lower doses, even when the higher doses are located on the descending limb of the inverted-U-shaped dose–response curve.

The first relevant observation that relates to this matter is that responding maintained by higher drug doses is less disrupted by increases in response requirement than is responding at lower doses. Studies of oral pentobarbital self-administration by rhesus monkeys have shown that increasing the FR value shifts the inverted-U-shaped dose–response curve to the right (Lemaire & Meisch, 1984). With increases in the FR value, lower pentobarbital doses no longer maintain responding, and there is a progressive increase in the dose that maintains the highest rate of responding. An important observation is that the percentage decrease from baseline in the number of drug deliveries is less at higher doses than at lower doses. In other words, when response requirement is increased, responding maintained by higher doses is more persistent relative to baseline than responding maintained by lower doses. This finding illustrates a basic principle that relative persistence of behavior across increases in schedule size is positively correlated with the magnitude of the reinforcer maintaining responding (Lemaire & Meisch, 1984; Meisch, 2000).

A second line of evidence that suggests that higher doses are more reinforcing than lower doses comes from drug self-administration studies in which there is concurrent access to two drug doses. The general finding is that in studies with rhesus monkeys the larger of the two drug doses is preferred. This is the case for experiments using the intravenous route of drug self-administration with psychomotor stimulants (Iglauer, Llewellyn, & Woods, 1975; Iglauer & Woods, 1974; Johanson, 1975; Johanson & Schuster, 1975). It is also the case in studies with orally self-administered drugs such as pentobarbital (Meisch & Lemaire, 1988, 1989; Meisch, Lemaire, & Cutrell, 1992), cocaine (Meisch & Stewart, 1995), and methadone (Meisch, Stewart, & Wang, 1996). In a study with rats, choice between different ethanol concentrations was examined under a concurrent FR 8 FR 8 schedule (Samson, Pfeffer, & Tolliver, 1988). Responding on one lever resulted in the presentation of 10% (vol/vol) ethanol, and responding on the second lever resulted in the presentation of 5%, 20%, or 40% (vol/vol) ethanol. The locations of the solutions were alternated daily. The comparisons of the ethanol concentrations were confounded by a side preference, however, and responding on that side was always greater regardless of the ethanol solutions present. Although no clear ethanol concentration preferences were noted, the relative rate of responding on the preferred side when 10% ethanol was presented on that side decreased significantly as the ethanol concentration increased at the nonpreferred side.

The present two experiments extended this previous work by examining the relative reinforcing effects of different doses of orally self-administered ethanol in rhesus monkeys. Dose was manipulated by changing the concentration of the ethanol solution, while the volume delivered at the completion of each response requirement was held constant.

The first experiment examined persistence of responding maintained by deliveries of different ethanol concentrations under FR schedules. The FR value was increased while responding maintained by different ethanol concentrations was measured. Although interactions between concentration and schedule value have been examined in self-administration studies with pentobarbital (Lemaire & Meisch, 1984, 1985, 1991) and cocaine (Macenski & Meisch, 1998), interactions between schedule value and reinforcer magnitude have not been investigated with ethanol. Most nonhuman primate studies with ethanol have focused on a single variable such as ethanol concentration (Henningfield & Meisch, 1978), schedule size (Henningfield & Meisch, 1976b), feeding conditions (Rodefer & Carroll, 1996), and drug effects (Boyle et al., 1998; Rodefer, Campbell, Cosgrove, & Carroll, 1999; Williams, Winger, Pakarinen, & Woods, 1998). Similarly, in rodent studies of ethanol reinforcement, the examination of interactions between variables is uncommon;

the main concern has been with drug effects, strain differences, and the neuropharmacology of ethanol reinforcement (Samson, 2000; Samson & Hodge, 1996).

The second experiment used a concurrent-choice procedure in which two ethanol concentrations were available at the same time. The effect of varying the FR response requirement on choice between different concurrently available ethanol concentrations also was examined. The objective was to examine the relations among relative and absolute response rates and reinforcer magnitude under conditions of access to either one or two concentrations of ethanol.

GENERAL METHOD

Subjects

Three adult male rhesus monkeys (*Macaca mulatta*) were used. Each had a history of oral drug self-administration. Monkey M-EG had previously self-administered cocaine, etonitazene, and ethanol. Monkeys M-CC and M-A had histories of oral barbiturate, benzodiazepine, and ethanol self-administration. They were housed in a temperature-controlled room with a 12:12 hr light/dark cycle (lights on at 7:00 a.m.) and were maintained at reduced body weights by daily feeding of a measured amount of commercially available chow (Lab Diet™ high-protein monkey diet #5045; PMI Feeds, St. Louis, MO) plus fresh fruit (180 g) and a multiple vitamin tablet. Between the sessions, water was available 18 hr a day. At the beginning of the study, the weights and percentage of free-feeding body weights of the subjects were as follows: M-A: 8.36 kg, 89%; M-CC: 9.81 kg, 85%; M-EG: 9.19 kg, 75%. Food restriction increases alcohol- and drug-reinforced behavior (Carroll & Meisch, 1984) and prevents obesity that can occur when monkeys are housed singly with unlimited access to food. The feeding regimen for each of the monkeys was determined largely by the health and appearance of the individual subjects. For example, although M-EG's body weight was reduced the most in terms of percentage of its free-feeding body weight, this monkey was initially more obese than the others.

Drugs

To prepare the ethanol solutions, 95% vol/vol ethanol was diluted in tap water on the day preceding the experimental session and stored in sealed flasks until used. For example, 500 ml of 8% (wt/vol) ethanol was prepared by mixing 53 ml of 95% ethanol with enough water to produce a total volume of 500 ml. All solutions were at room temperature at the start of sessions.

Apparatus

The experiment was controlled and monitored with SKED™ software (State Systems), running on a DEC PDP-11 computer located near the room containing the experimental chambers. Subjects were individually housed in stainless-steel cages (76 cm by 102 cm by 81 cm; Lab Products, Inc., Maywood, NJ) 24 hr per day. A liquid-delivery work panel (Kandota Instruments, Sauk Centre, MN) was attached to the outside of one side wall, and spouts fastened to the panel protruded into the cage through holes cut in that wall. Attached to the back of the work panel was a T-shaped bar, on each limb of which was fastened a stainless-steel reservoir covered with a lid to prevent evaporation. Liquids contained in each reservoir passed via polyethylene tubing to a solenoid-operated valve at the rear of one of two brass spouts. These spouts (1.2 cm outside diameter, 0.2 cm inside diameter) protruded 2 cm into the cage, 64 cm above the floor and 15.5 cm either side of midline. The spouts served as operanda for operant responses, which were mouth contacts with either spout. At each liquid delivery, the solenoid was activated for a maximum of 150 ms, allowing approximately 0.67 ml of liquid to pass through the spout and into the monkey's mouth. That the response was made by lip contact was verified by observers periodically monitoring behavior through closed-circuit television and by observers in the room housing the experimental chambers. More extensive details of the liquid-delivery apparatus are described elsewhere (Gieske, 1978; Henningfield & Meisch, 1976a). Between sessions, water was delivered from one of the two spouts used during the sessions. The spout from which the water was available alternated from left to right on a daily basis.

Above each spout (12 cm) was a green jewel-covered 2.8-W stimulus light that extended 2 cm into the cage. These stimulus lights were used as discriminative stimuli for the availability of liquids, as described below.

Spouts were embedded in Plexiglas disks, which covered the holes (7 cm diameter) in the cage wall through which the spouts entered. Behind the Plexiglas disks were four 1.1-W lights, which were distributed evenly around, and 2.5 cm from, the spout in an X pattern. Two of the spout lights were capped with green translucent lenses, and the other two had white lenses. The purpose of these spout lights was to provide an exteroceptive stimulus change with each response.

Procedure

Daily 3-hr sessions were conducted from 11:00 a.m. to 2:00 p.m. Immediately before the sessions was a 1-hr timeout during which no liquids were available. At that time, the volume of water remaining was recorded and used to calculate the volume of water consumed during the period between sessions. Next, liquids appropriate for the session were placed in the reservoirs. During the experimental sessions, a fixed number of contacts on a spout was required for reinforcement (i.e., delivery of 0.67 ml of liquid was concomitant with the final contact). Thus, unlike most FR schedules, the operant and the consummatory responses were formally the same. The FR schedules for each of the two spouts operated independently and were set at values from FR 8 to FR 128 (see below). Changes from one experimental condition to the next (e.g., changes in the ethanol concentration or the FR value) were made after six consecutive sessions of stable behavior. Stability of responding was determined by visual inspection of the daily data and was defined as the occurrence of six consecutive sessions in which numbers of deliveries of each of the two concurrently available liquids showed no increasing or decreasing trends. The positions of the two liquids alternated from left to right on a daily basis. Therefore, when the mean liquid deliveries were calculated, three of the six data points were from sessions in which the liquid was on the left and three of the data points were from sessions in which the liquid was on the right.

Timeouts also occurred for the 1st hour after the session and for the 3rd hour after the session. During the first of these, data from the session were collected. Water was placed in one of each monkey's reservoirs for the period between sessions. During the second postsession timeout, the monkeys were fed. The green stimulus light above one spout was steadily illuminated, and water was available under an FR 1 reinforcement schedule from that spout. The spout's white-lensed spout lights were illuminated for the duration of each mouth contact.

EXPERIMENT 1

The purpose of this experiment was to examine the interaction between two variables: FR size and ethanol concentration.

Method

One rhesus monkey (M-A) served as the subject. A series of six concentration–response tests was conducted, each under a different FR response requirement. For each dose–response test, the available ethanol concentrations were 32%, 8%, and 2% (wt/vol). Then there was a retest of the 32% concentration. Water was concurrently available from the second spout. For each dose–response test, the FR requirement was 8, 16, 32, 64, and then 128, followed by a return to FR 8.

Results and Discussion

Figure 1 shows that response rate first increased and then decreased as a function of increases in FR requirement. Figure 1 also shows that ethanol deliveries decreased as a function of increases in the FR response requirement. The rate of decrease differed among the three ethanol concentrations, however. Deliveries of the lowest concentration (2%) decreased markedly when the FR requirement increased from FR 8 to FR 16. Deliveries of higher concentrations were affected only at higher FR values. The ethanol concentration at which the greatest number of deliveries was obtained depended on the value of the FR schedule. Thus, at FR 8, deliveries of 2% ethanol were the greatest. At FR 16 and FR 32, deliveries of 8% ethanol were the greatest, and at FR 64 and 128, deliveries of 32% ethanol were the greatest. (The scale of Figure 1 obscures the fact that

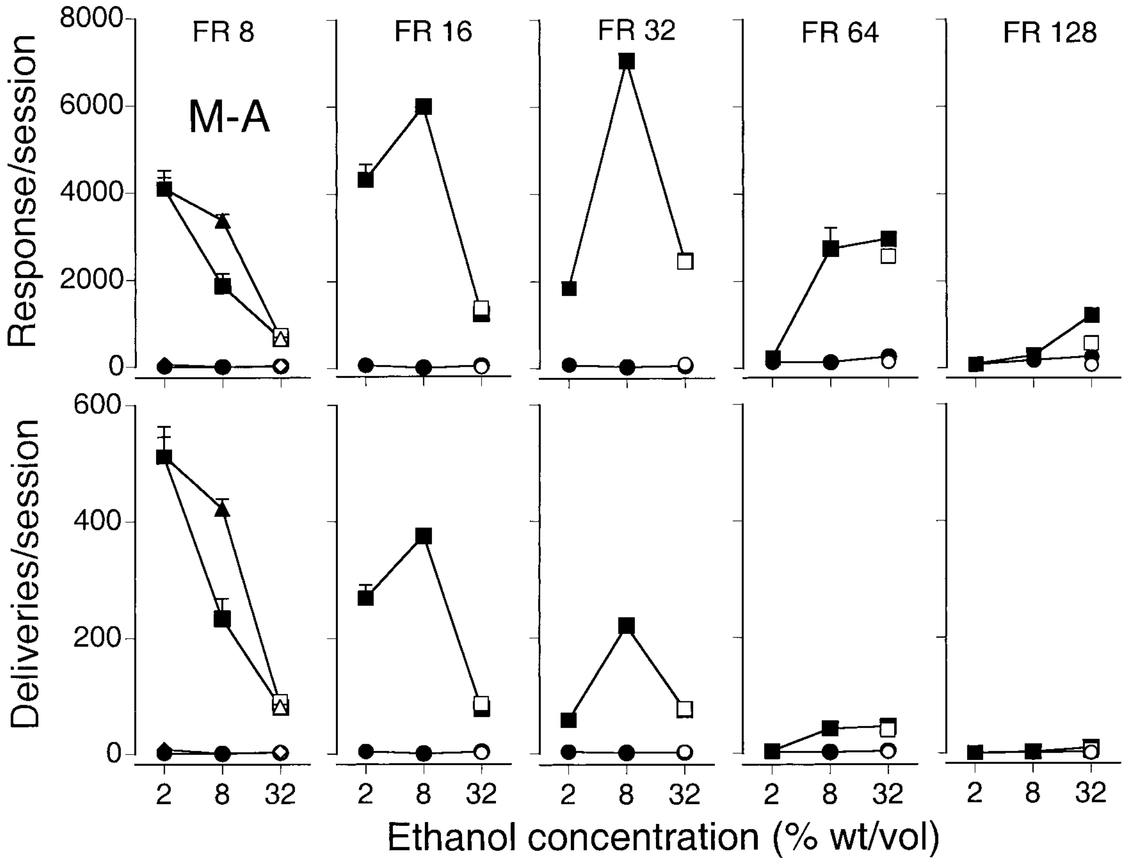

Fig. 1. Oral ethanol-maintained responses (upper panels) and deliveries (lower panels) by 1 rhesus monkey (M-A) as a function of increases in the FR requirement. Each point shows the number of responses or deliveries of 0.67-ml liquid per 3-hr session maintained by ethanol (solid squares or triangles) and water (circles or diamonds). The data are the mean (± *SEM*) of six consecutive sessions of stable responding. At each FR value the three ethanol concentrations were tested in descending order (squares) followed by a retest of the 32% concentration (open symbols). The absence of error bars indicates that the *SEM* was sufficiently small to be covered completely by the symbol.

at FR 128 the mean number ± *SEM* of ethanol deliveries for the three concentrations was as follows: 2%: 0.33 ± 0.23; 8%: 2.0 ± 0.75; 32%: 9.33 ± 2.51.) The values for the retest sessions at 32% ethanol replicated the values for the initial sessions at 32% (Figure 1), indicating that there was no shift in ethanol drinking as a function of time or experience. At most concentrations and FR sizes, the number of ethanol responses and deliveries far exceeded the number of water responses and deliveries. Only at FR 64 and FR 128 were there overlaps in the ranges of ethanol and water values.

Table 1 lists the number of sessions and ethanol intake (grams of ethanol consumed per kilogram of body weight) at each condition. The mean number of sessions at each condition was 6.9 (range, 6 to 10). In general, ethanol intake decreased as concentration decreased. Similar findings have been observed in related studies when ethanol concentration was varied (Henningfield & Meisch, 1978; Meisch, Henningfield, & Thompson, 1975). In parallel with the number of liquid deliveries, ethanol intake also decreased as a function of FR size. When the FR 8 condition was repeated, ethanol intake was similar to initial values except at 8%, where intake was almost double the original value.

Figure 2 shows the data from Figure 1

Table 1

Ethanol intake and number of sessions in each condition for Monkey M-A.

Ethanol concentration (%)	FR size	Ethanol intake g/kg (± *SEM*)	Number of sessions
32 vs. 0	8	1.68 ± 0.09	6
8 vs. 0	8	1.29 ± 0.17	9
2 vs. 0	8	0.75 ± 0.07	10
32 vs. 0	8	2.07 ± 0.17	7
32 vs. 0	16	1.73 ± 0.01	7
8 vs. 0	16	2.13 ± 0.06	6
2 vs. 0	16	0.39 ± 0.03	6
32 vs. 0	16	1.80 ± 0.10	6
32 vs. 0	32	1.62 ± 0.03	8
8 vs. 0	32	1.35 ± 0.06	6
2 vs. 0	32	0.09 ± 0.00	7
32 vs. 0	32	1.85 ± 0.08	6
32 vs. 0	64	1.07 ± 0.04	7
8 vs. 0	64	0.27 ± 0.06	7
2 vs. 0	64	0.00 ± 0.00	6
32 vs. 0	64	0.90 ± 0.04	6
32 vs. 0	128	0.30 ± 0.04	6
8 vs. 0	128	0.01 ± 0.00	7
2 vs. 0	128	0.00 ± 0.00	6
32 vs. 0	128	0.11 ± 0.04	6
32 vs. 0	8	1.80 ± 0.07	7
8 vs. 0	8	2.47 ± 0.11	10
2 vs. 0	8	0.75 ± 0.05	8
32 vs. 0	8	1.76 ± 0.10	6

transformed so that the number of responses and ethanol deliveries at each FR value is expressed as a percentage of the number of deliveries obtained at FR 8; that is, the number of 2%, 8%, and 32% ethanol deliveries received under the FR 8 schedule was set to be the 100% value for those concentrations. Figure 2 indicates that increasing the FR response requirement usually was accompanied by a decrease in the percentage of baseline (FR 8) deliveries obtained. An exception was responding maintained by 8% ethanol, which increased when the FR value increased from FR 8 to FR 16. Figure 2 shows that the degree of reduction that occurred when the FR was increased depended on the concentration of the ethanol solution. The reduction in the percentage of baseline deliveries of 2% ethanol was considerable at FR 16. Reduction of 8% and 32% ethanol-maintained responding did not occur until the imposition of an FR 64 schedule. At FR 64 and FR 128, however, the percentage of baseline responding maintained by 8% ethanol was reduced by a greater percentage than was responding maintained by 32% ethanol.

The results are consistent with earlier studies of interactions between FR size and pentobarbital concentration (Lemaire & Meisch, 1984), cocaine concentration (Macenski & Meisch, 1998), and food magnitude (Kliner, Lemaire, & Meisch, 1988). In these studies, as FR size increased, the magnitude of the reinforcer that maintained peak responding also increased. The outcome of Experiment 1 shows that the relative persistence of responding increases with increases in ethanol concentration and suggests that the relative reinforcing effects of ethanol are a direct function of concentration.

EXPERIMENT 2

If the relative reinforcing effects of ethanol are a direct function of concentration, then higher concentrations should be preferred to lower concentrations. This possibility was examined by making pairs of ethanol concentrations available under concurrent FR FR schedules.

Method

Two monkeys (M-CC and M-EG) served as subjects. Experiment 2 was carried out in two consecutive test series that consisted of two and three phases, respectively.

Test Series 1

In Phase 1 concentration–response functions were determined with ethanol solution and water available under concurrent FR 16 FR 16 schedules of reinforcement. Three ethanol concentrations (4%, 8%, and 16% wt/vol) were tested in descending order followed by a second test at the 16% concentration. Water was always available from the second spout. In Phase 2 the relative reinforcing effects of different concurrently available concentrations were determined using a choice procedure. One ethanol concentration was available from one liquid-delivery system, and a different ethanol concentration was concurrently available from the other. The following ethanol concentration comparisons were made: 16% versus 4%, 16% versus 8%, and 8% versus 4%. To detect possible order or sequence effects, the 16% versus 4% and 16% versus 8% choice tests were repeated.

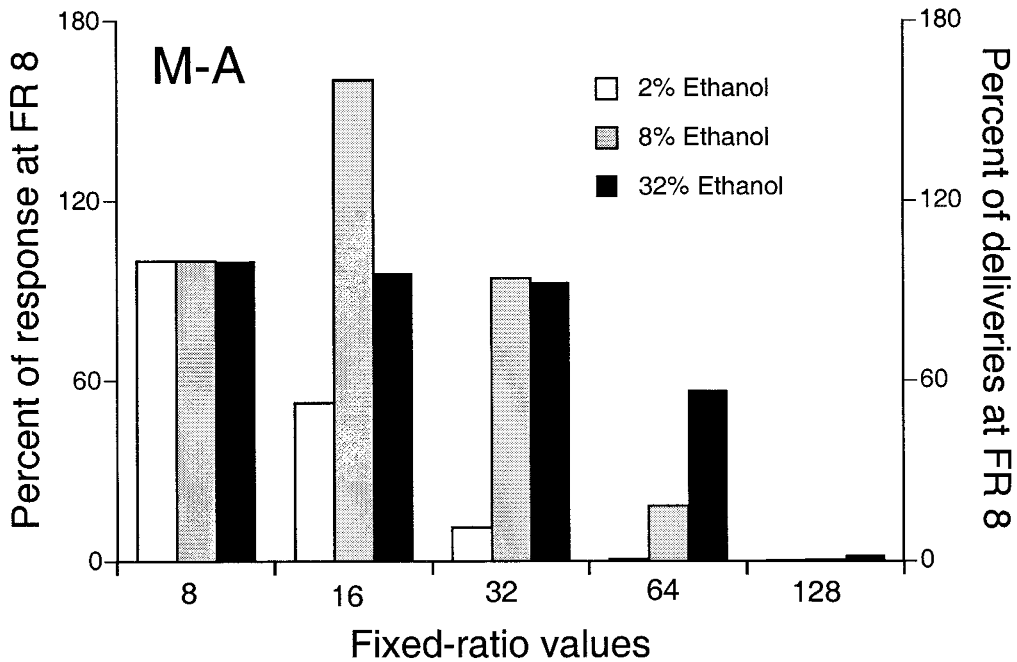

Fig. 2. Differential persistence of responding by Monkey M-A maintained by different ethanol concentrations as a function of increases in the FR response requirement. For this figure, the data shown in Figure 1 were transformed so that the number of responses and ethanol deliveries at each FR value are expressed as a percentage of the number of deliveries obtained at FR 8. That is, the numbers of 2%, 8%, and 32% ethanol deliveries received under the FR 8 schedule were set at 100%. Then the number of 2%, 8%, and 32% ethanol deliveries received under the FR 16, 32, 64, and 128 schedules were recast as a percentage of their corresponding FR 8 values. Note that the left ordinate for responses is identical to the right ordinate for deliveries.

Test Series 2

Phase 1 and Phase 2 of this series were similar to those for Test Series 1 except that the ethanol concentrations available under concurrent FR 16 FR 16 schedules were 2%, 8%, and 32%. In Phase 1, single ethanol concentrations and water were concurrently available. In Phase 2, two ethanol concentrations were concurrently available, and the following comparisons were made: 32% versus 2%, 32% versus 8%, 8% versus 2%, 32% versus 2% (retest), and 32% versus 8% (retest). Phase 3 consisted of examination of the effect of varying the FR response requirement on concurrent choice between 32% and 8% ethanol. Thus, 32% and 8% ethanol both continued to be available while FR 16, FR 32, and FR 64 were tested in ascending order and then in descending order followed by a single test at FR 8. Finally, FR 16, FR 32, and FR 64 were tested in ascending and descending order for a second time.

RESULTS AND DISCUSSION

Test Series 1

Figure 3 shows the results comparing 4%, 8%, and 16% ethanol under FR 16 when the concentrations were tested with water concurrently available. For both monkeys, ethanol-maintained responding always exceeded responding maintained by water. At the 16% ethanol concentration, the initial test and the retest points were similar. The ethanol concentration–response functions showed an inverted-U shape; the highest rate of responding was at the 8% concentration. Ethanol intake (grams per kilogram) during the same sessions was an ascending function of the available ethanol concentration (Figure 3).

Figure 4 shows the number of responses in the same 2 monkeys during the second phase when different pairs of ethanol concentrations were concurrently available under FR 16 schedules. In all cases, the higher of the two concentrations maintained the higher

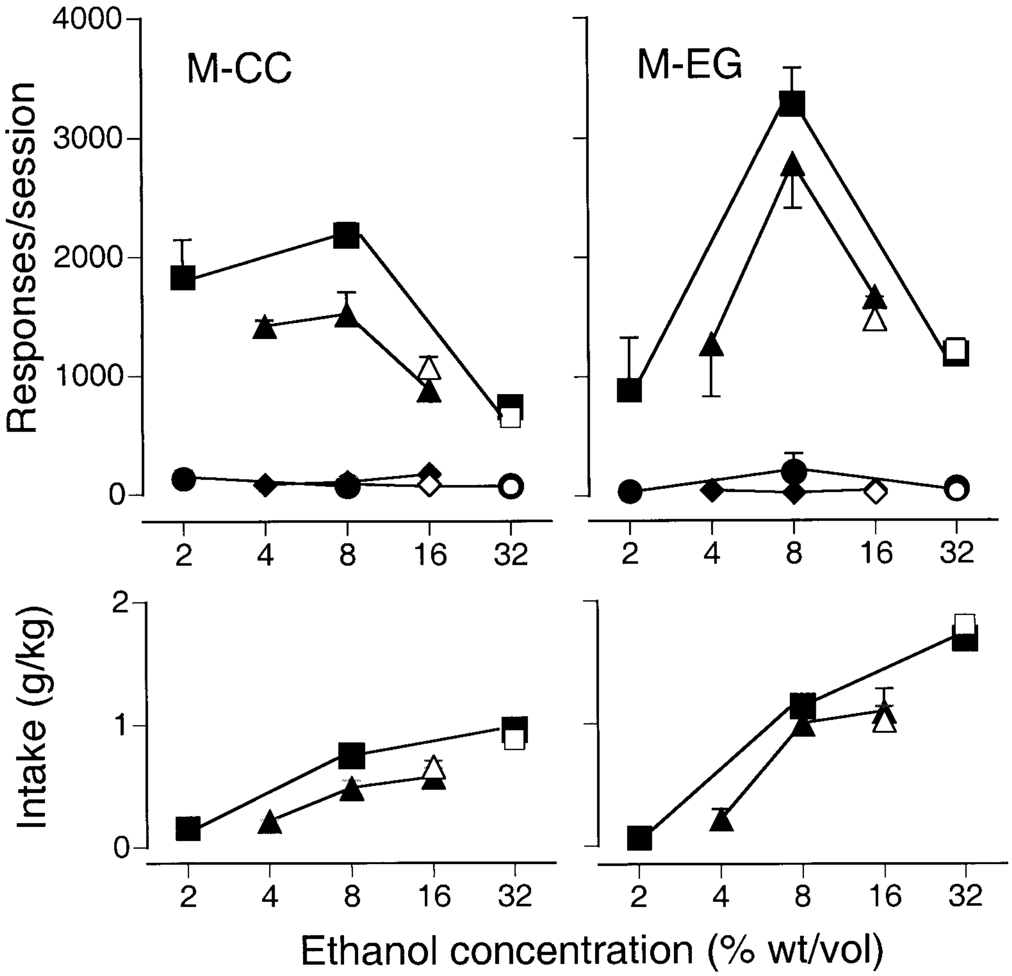

Fig. 3. Results for Test Series 1 comparing 4%, 8%, and 16% ethanol, and results for Test Series 2 comparing 2%, 8%, and 32% ethanol. Upper panels show the number of responses per 3-hr session maintained by ethanol (filled triangles for Test Series 1 and filled squares for Test Series 2) and water (filled diamonds for Test Series 1 and filled circles for Test Series 2) in 2 rhesus monkeys (M-CC and M-EG). The data are the mean (± *SEM*) of six consecutive sessions of stable behavior. The concentrations were tested in descending order followed by a second determination of values at 16% and 32% concentrations (open symbols). Lower panels show ethanol intake during the same sessions. The absence of error bars indicates that the *SEM* was sufficiently small to be covered completely by the symbol.

rate of responding. The second determination of comparisons between 16% and 8% and between 16% and 4% yielded results similar to the initial comparisons, in that the higher concentration maintained higher response rates. For both the initial and second determinations, the differences between 16% and 4% were greater than the differences between 16% and 8%. Such a result is to be expected, given that the comparison between 8% and 4% showed higher rates maintained by 8%.

Test Series 2

Figure 3 shows the results for the series comparing 2%, 8%, and 32% ethanol with water concurrently available on FR 16 schedules. For both monkeys, ethanol-maintained responding always exceeded responding maintained by concurrently available water. The concentration–response functions again were an inverted-U shape, with the 8% concentration maintaining the highest rate of responding. At the 32% ethanol concentration,

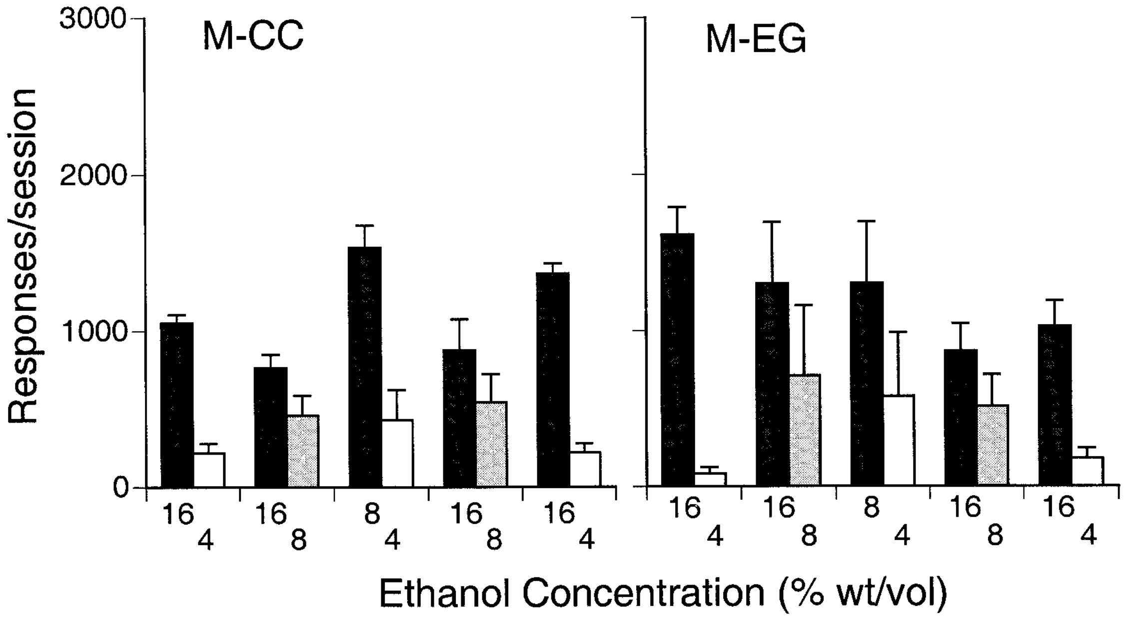

Fig. 4. Results for Test Series 1 comparing preferences between pairs of ethanol concentrations at FR 16. The numbers of responses per 3-hr session are illustrated for three pairs of ethanol concentrations: 16% and 4%, 16% and 8%, and 8% and 4% in Monkeys M-CC and M-EG. A second determination of values for two pairs of concentrations is also shown (16% and 8%, and 16% and 4%). Black bar: 16%; gray bar: 8%; white bar: 4%. The data are the mean (± *SEM*) of six consecutive stable sessions.

the test and the retest values were similar. Ethanol intake during the same sessions was an ascending function of the available ethanol concentration (Figure 3).

Figure 5 shows the number of responses for the same 2 monkeys when different pairs of ethanol concentrations were concurrently available at FR 16. Higher rates of responding were maintained by the higher of the two concentrations for the 32% versus 2% and the 8% versus 2% comparisons, but 8% ethanol maintained higher rates of responding than 32% when those two ethanol concentrations were concurrently available. The second determination of comparisons between 32% and 2% and between 32% and 8% yielded results similar to the initial comparisons. The difference between 8% and 2% was greater than the differences between 32% and 2%. Such a result is to be expected, given that the comparison between 8% and 32% showed higher rates maintained by 8%.

Figure 6 shows the effects of varying the FR response requirement on concurrent choice between 32% and 8% ethanol. At FR 8 and FR 16, higher rates of responding were maintained by the 8% ethanol than by 32% ethanol for both monkeys. This replicated the results described immediately above. At FR 32, M-EG showed a reversal in the relative preference for the two concentrations so that the higher (32%) ethanol concentration maintained more responding than the lower (8%) ethanol concentration. For M-CC, at FR 32 the relative preference for the two ethanol concentrations depended on the sequence or order of testing: The first test at FR 32 showed a clear preference for the 8% ethanol, the second test showed a preference for 32% ethanol, and the third and fourth tests showed about equal responding maintained by 8% and 32% ethanol. When the FR response requirement was 64, however, both monkeys showed more responding maintained by the 32% concentration than by the 8% concentration. An exception was the second test at FR 64 for M-EG, when responses maintained by both ethanol concentrations were equal and unusually low, perhaps due to a general deterioration of responding at the high FR (i.e., ratio strain). This monkey's responding recovered, however, when the FR value subsequently was reduced to 32, and a

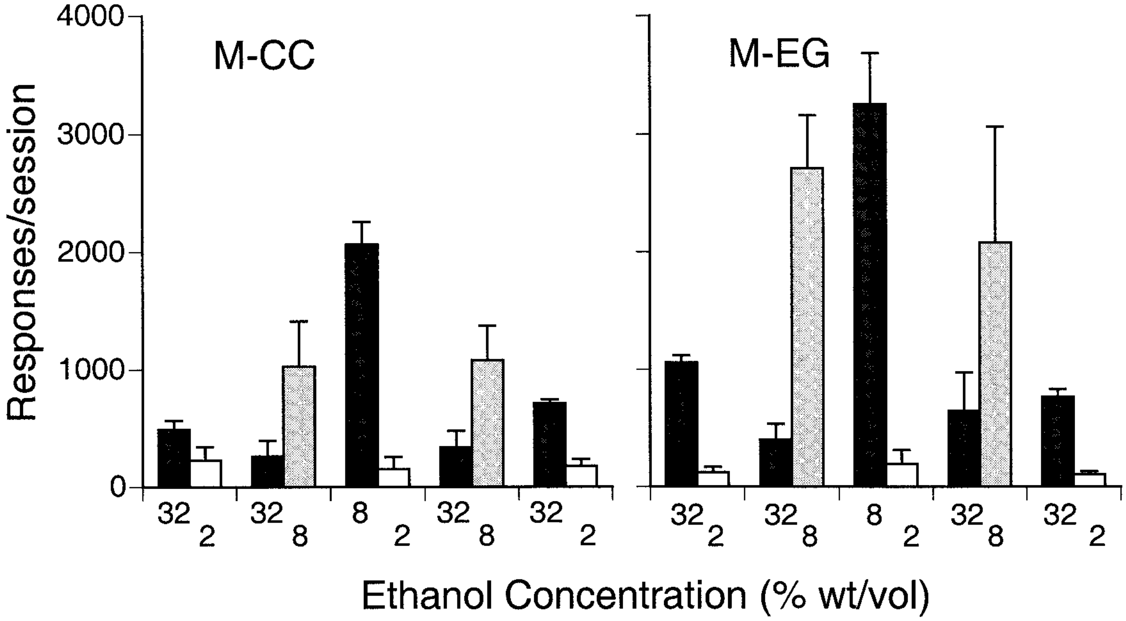

Fig. 5. Results for Test Series 1 comparing preferences between pairs of ethanol concentrations at FR 16. The numbers of responses per 3-hr session are shown for three pairs of ethanol concentrations: 32% and 2%, 32% and 8%, and 8% and 2% in Monkeys M-CC and M-EG. A second determination of values for two pairs of concentrations is also shown (32% and 8%, and 32% and 2%). Black bar: 32%; gray bar: 8%; white bar: 2%. The data are the mean (± *SEM*) of six consecutive stable sessions.

clear preference for the higher of the two ethanol concentrations again was seen.

Tables 2 and 3 list the ethanol intake and number of sessions at each condition for Monkeys M-EG and M-CC, respectively. The mean number of sessions at each condition was 8.4 for M-EG (range, 6 to 15) and 7.2 for M-CC (range, 6 to 12). When a single concentration of ethanol was present, ethanol intake increased as ethanol concentration increased. When two ethanol concentrations were concurrently present, the higher concentration generally contributed more to the total intake. The total intake of a pair of concentrations can be compared with that of the higher concentration studied alone. For both monkeys, the intake of 16% ethanol was not systematically greater than intake of combinations of 16% plus another concentration. Intake of 32% ethanol was greater when studied alone, however, relative to being concurrently present with another concentration. At FR 16, there were a total of eight comparisons when 32% was concurrently available with another concentration (either 8% or 2%). For seven of these eight comparisons, M-CC's intake of 32% ethanol, when studied alone, was greater than the total intake of 32% plus that of the second concentration. M-EG's intake of 32%, when studied alone, was always greater than the combined intake of 32% and a second concentration. Thus, presence of another ethanol concentration decreased intake of 32% ethanol, and the decrease was greater when 8% ethanol was present than when 2% ethanol was available (Tables 2 and 3).

The intakes listed in Tables 1, 2, and 3 can be compared with intakes and blood ethanol levels at the same concentrations that were reported in an earlier study (Henningfield & Meisch, 1978). Blood samples were obtained at the end of 3-hr sessions, and ethanol levels were determined. The ethanol intakes at concentrations of 8%, 16%, and 32% were 2.56, 2.72, and 3.08 g/kg. These intakes are greater than those seen in the present study, and they resulted in blood levels with means that ranged from 207 to 265 mg/dl. Although the intakes in the present study were lower, it is reasonable to conclude that they also would have produced substantial blood ethanol lev-

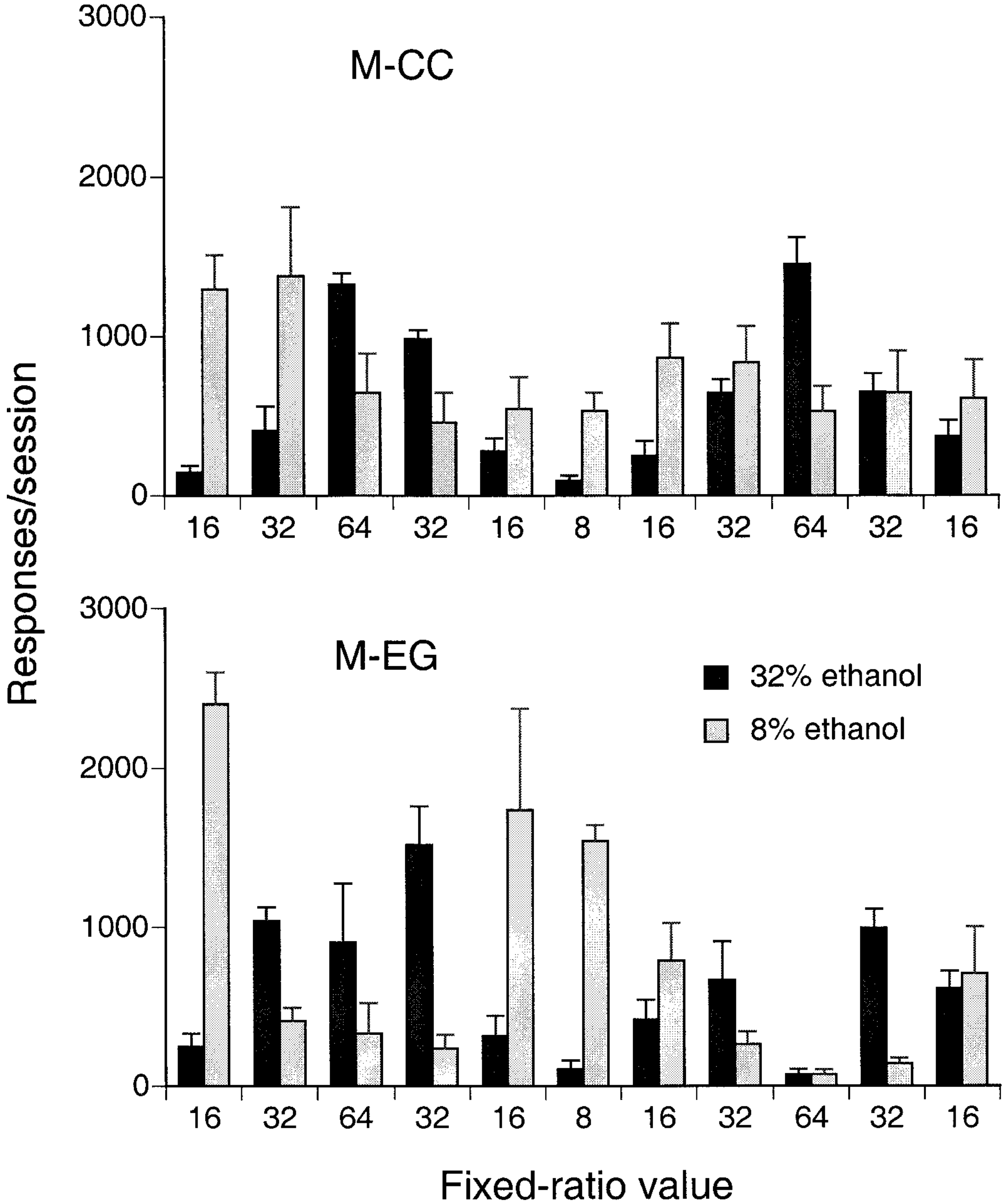

Fig. 6. The effects of varying the FR requirement on concurrent choice between 32% and 8% ethanol. The bar graphs show the number of responses for Monkeys M-CC and M-EG when 32% and 8% ethanol concentrations were concurrently available. The FR requirement was varied in the sequence shown from left to right on the abscissa. The data are the mean (± *SEM*) of six consecutive sessions of stable behavior.

els and corresponding pharmacological effects.

At the end of these experiments when ethanol was no longer available, signs of withdrawal were not observed and were not anticipated because access to ethanol had been limited to 3 hr each day.

GENERAL DISCUSSION

In both Experiments 1 and 2, when an ethanol solution and water were available concurrently, the number of ethanol deliveries consistently exceeded the number of water deliveries. Thus, ethanol functioned as a pos-

Table 2

Ethanol intake and number of sessions in each condition for Monkey M-EG.

Condition (%)	FR size	Ethanol intake (g/kg of body wt ± *SEM*) Higher ethanol concentration	Lower ethanol concentration	Higher + lower concentrations	Sessions
16 vs. 0	16	1.10 ± 0.16	0.00 ± 0.00	1.10 ± 0.16	8
8 vs. 0	16	1.00 ± 0.11	0.00 ± 0.00	1.00 ± 0.11	6
4 vs. 0	16	0.22 ± 0.08	0.00 ± 0.00	0.22 ± 0.08	6
16 vs. 0	16	1.02 ± 0.11	0.00 ± 0.00	1.02 ± 0.11	7
16 vs. 4	16	1.08 ± 0.09	0.01 ± 0.01	1.09 ± 0.10	14
16 vs. 8	16	0.88 ± 0.22	0.21 ± 0.12	1.09 ± 0.30	15
8 vs. 4	16	0.43 ± 0.12	0.03 ± 0.02	0.46 ± 0.13	9
16 vs. 8	16	0.59 ± 0.10	0.18 ± 0.07	0.77 ± 0.11	9
16 vs. 4	16	0.70 ± 0.09	0.03 ± 0.01	0.73 ± 0.09	6
32 vs. 0	16	1.69 ± 0.14	0.00 ± 0.00	1.69 ± 0.14	8
8 vs. 0	16	1.14 ± 0.07	0.00 ± 0.00	1.14 ± 0.07	6
2 vs. 0	16	0.07 ± 0.03	0.00 ± 0.00	0.07 ± 0.03	7
32 vs. 0	16	1.80 ± 0.11	0.00 ± 0.00	1.80 ± 0.11	6
32 vs. 2	16	1.47 ± 0.09	0.01 ± 0.00	1.48 ± 0.09	7
32 vs. 8	16	0.46 ± 0.15	0.94 ± 0.12	1.40 ± 0.24	14
8 vs. 2	16	1.12 ± 0.14	0.01 ± 0.01	1.13 ± 0.14	9
32 vs. 8	16	0.90 ± 0.42	0.73 ± 0.32	1.63 ± 0.73	12
32 vs. 2	16	1.09 ± 0.08	0.00 ± 0.00	1.09 ± 0.08	9
32 vs. 8	16	0.29 ± 0.13	0.79 ± 0.06	1.08 ± 0.15	6
32 vs. 8	32	0.56 ± 0.14	0.06 ± 0.02	0.62 ± 0.13	7
32 vs. 8	64	0.18 ± 0.12	0.01 ± 0.01	0.19 ± 0.13	8
32 vs. 8	32	1.00 ± 0.10	0.01 ± 0.01	1.01 ± 0.12	7
32 vs. 8	16	0.40 ± 0.19	0.59 ± 0.21	0.99 ± 0.39	10
32 vs. 8	8	0.17 ± 0.11	1.04 ± 0.06	1.21 ± 0.14	9
32 vs. 8	16	0.63 ± 0.23	0.28 ± 0.07	0.91 ± 0.23	9
32 vs. 8	32	0.37 ± 0.18	0.01 ± 0.01	0.38 ± 0.19	6
32 vs. 8	64	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	9
32 vs. 8	32	0.64 ± 0.08	0.01 ± 0.01	0.65 ± 0.08	8
32 vs. 8	16	0.82 ± 0.14	0.24 ± 0.10	1.06 ± 0.23	15

itive reinforcer. The observed levels of ethanol intake and the temporal pattern of ethanol-reinforced responding were consistent with previous reports of oral ethanol self-administration by rhesus monkeys (Meisch, 1977, 1984; Meisch & Stewart, 1994).

In Experiment 1, the overall effect of increasing the FR value was to decrease ethanol-maintained responding, but the degree of decrease depended on the ethanol concentration. Responding at higher ethanol concentrations was less altered by increases in the response requirement than at lower ethanol concentrations. Similar results previously have been observed when different concentrations of orally self-administered pentobarbital were tested in rhesus monkeys while the value of the FR reinforcement schedule was increased (Lemaire & Meisch, 1984, 1985, 1991). Studies using signaled differential-reinforcement-of-low-rate schedules with oral pentobarbital self-administration in rhesus monkeys (Lemaire & Meisch, 1991) and multiple extinction *x*-s FR 1 schedules with oral ethanol self-administration in rats (Beardsley, Lemaire, & Meisch, 1993) also have shown that behavior maintained by higher drug doses was more persistent when the interreinforcer interval was increased than was behavior maintained by lower doses. The results of Experiment 2 were consistent with the results of Experiment 1 in showing that higher concentrations were more reinforcing than lower concentrations. That is, when pairs of concentrations were made available at the same time, the higher concentration usually maintained more responding than the lower concentration.

The results of the present study suggest that response rates measured when single ethanol concentrations are tested sequentially with water concurrently available do not always predict which concentrations will maintain the greatest response rates when

Table 3

Ethanol intake and number of sessions in each condition for Monkey M-CC.

Condition (%)	FR size	Ethanol intake (g/kg of body wt ± *SEM*) Higher ethanol concentration	Lower ethanol concentration	Higher + lower concentrations	Sessions
16 vs. 0	16	0.58 ± 0.06	0.00 ± 0.00	0.58 ± 0.06	7
8 vs. 0	16	0.49 ± 0.05	0.00 ± 0.00	0.49 ± 0.05	12
4 vs. 0	16	0.22 ± 0.01	0.00 ± 0.00	0.22 ± 0.01	8
16 vs. 0	16	0.66 ± 0.04	0.00 ± 0.00	0.66 ± 0.04	6
16 vs. 4	16	0.68 ± 0.04	0.03 ± 0.01	0.71 ± 0.04	6
16 vs. 8	16	0.47 ± 0.07	0.15 ± 0.05	0.62 ± 0.09	6
8 vs. 4	16	0.44 ± 0.05	0.06 ± 0.03	0.50 ± 0.08	7
16 vs. 8	16	0.63 ± 0.19	0.16 ± 0.05	0.79 ± 0.24	7
16 vs. 4	16	0.80 ± 0.06	0.03 ± 0.01	0.83 ± 0.07	6
32 vs. 0	16	0.96 ± 0.05	0.00 ± 0.00	0.96 ± 0.05	8
8 vs. 0	16	0.75 ± 0.03	0.00 ± 0.00	0.75 ± 0.03	6
2 vs. 0	16	0.16 ± 0.03	0.00 ± 0.00	0.16 ± 0.03	6
32 vs. 0	16	0.88 ± 0.07	0.00 ± 0.00	0.88 ± 0.07	8
32 vs. 2	16	0.69 ± 0.10	0.02 ± 0.01	0.71 ± 0.10	6
32 vs. 8	16	0.35 ± 0.19	0.33 ± 0.13	0.68 ± 0.28	7
8 vs. 2	16	0.70 ± 0.06	0.01 ± 0.01	0.71 ± 0.06	7
32 vs. 8	16	0.46 ± 0.18	0.35 ± 0.09	0.81 ± 0.25	9
32 vs. 2	16	0.97 ± 0.04	0.02 ± 0.01	0.99 ± 0.04	6
32 vs. 8	16	0.18 ± 0.09	0.43 ± 0.07	0.61 ± 0.13	6
32 vs. 8	32	0.25 ± 0.12	0.23 ± 0.08	0.48 ± 0.16	6
32 vs. 8	64	0.44 ± 0.05	0.02 ± 0.03	0.46 ± 0.04	6
32 vs. 8	32	0.64 ± 0.05	0.08 ± 0.03	0.72 ± 0.05	10
32 vs. 8	16	0.36 ± 0.14	0.18 ± 0.07	0.54 ± 0.15	8
32 vs. 8	8	0.20 ± 0.10	0.35 ± 0.07	0.55 ± 0.13	10
32 vs. 8	16	0.30 ± 0.15	0.30 ± 0.07	0.60 ± 0.18	10
32 vs. 8	32	0.36 ± 0.10	0.13 ± 0.04	0.49 ± 0.11	7
32 vs. 8	64	0.48 ± 0.06	0.04 ± 0.02	0.52 ± 0.07	7
32 vs. 8	32	0.39 ± 0.07	0.11 ± 0.05	0.50 ± 0.10	9
32 vs. 8	16	0.43 ± 0.14	0.20 ± 0.07	0.63 ± 0.19	9

different concentrations are presented in pairs. Specifically, when single ethanol concentrations were tested in Experiment 2 under FR 16 schedules, the highest rate of responding was always observed with 8% ethanol available. Higher ethanol concentrations maintained lower rates of responding than 8% ethanol when the concentrations were presented sequentially. These same high ethanol concentrations usually were preferred to 8% ethanol, however, in the choice tests when two different concentrations were presented concurrently at the FR 16 schedule value. In cases when this was not so, the relative preference for the two doses was reversed by increasing the FR response requirement. A similar reversal of preference with increases in FR value also was observed in a previous study of choice between different doses of orally delivered methadone (Meisch et al., 1996). In that experiment, under concurrent FR 16 schedules of reinforcement, 1 monkey showed greater responding maintained by a 0.2 mg/kg methadone solution than by a concurrently available 0.8 mg/kg methadone solution. When the FR value was increased to 32 and 64, however, the higher dose was preferred to the lower dose. A reversal of preference with increases in FR value also was observed with 2 of 4 monkeys in a study of choice between drug combinations (pentobarbital plus ethanol) and their components (pentobarbital alone or ethanol alone; Meisch & Lemaire, 1990). These findings demonstrate that one determinant of choice between two unequal reinforcers is the size of the response requirement. Such observations can be described with terminology from behavioral economics (e.g., Bickel, DeGrandpre, Higgins, & Hughes, 1990): Increases in the FR value result in an increase in price (ratio of reinforcer size to FR schedule value). It appears that as the prices become higher, the probability increases that the larger of two doses will be selected.

The inverted-U-shaped dose–response function seen with alcohol and other drugs has been interpreted in various ways. Although there is general agreement that the ascending part of the curve may represent increases in reinforcing effects with increases in the dose, the descending portion has been attributed to motor impairment, aversive taste, satiation, aversive effects, or decreases in reinforcing effectiveness (for reviews, see Katz, 1989; Meisch & Lemaire, 1993). None of these factors, however, appears to be a necessary condition under all circumstances for the production of an inverted-U-shaped function. For example, with regard to motor impairment, inverted-U-shaped concentration–response functions were observed with nondrug reinforcers such as sugar solutions that produce no motor impairment (e.g., Sclafani & Clyne, 1987). With regard to aversive taste, inverted-U-shaped functions were also seen with nonoral routes of drug administration, such as the intravenous route, in which taste is eliminated as a factor (Young & Herling, 1986). Decreases in the reinforcing effects of drugs do not account for the descending portion of the inverted-U-shaped dose–response curves, as suggested by the findings of the present investigation and previous studies (reviewed above).

With regard to satiation, interpretation of the descending portion of the dose–response curve is more complicated. Drug intake (in grams per kilogram) often continues to increase in a linear fashion over the same range of doses that comprise the descending portion of the dose–response curve, as in the present investigation (see Figure 3). Thus, it might seem that satiation is not a likely explanation for the descending portion of the curve. It is possible, however, that if the drug dose continued to increase, drug intake per session would reach an asymptotic plateau, above which it could not rise. Such an asymptote was observed in each of two previous studies in which reinforcer magnitude was varied by changing the number of reinforcer deliveries available after completion of each FR response sequence: One study varied the number of 45-mg food pellets available to rats after completion of the response requirement (Kliner et al., 1988); the other varied the number of deliveries of a constant-concentration drug solution that was available (Lemaire & Meisch, 1985). In both studies, as reinforcer magnitude increased, the number of reinforcer deliveries per session (and thus food intake or drug intake) eventually reached a plateau, above which it did not rise (Figures 2, 3, and 5 in Kliner et al., 1988; Figures 2 and 4 in Lemaire & Meisch, 1985). Thus, although the physiological mechanisms that limit intake of food and drug presumably are quite different, an upper bound was reached in both cases in the amount of reinforcer ingested. It is under just such conditions that the term *satiation* might be used to account for the descending portion of the dose–response curve (i.e., such conditions define *satiation*). In general, interpretation of the inverted-U-shaped dose–response functions obtained in different studies is difficult because these functions may result from different mechanisms when different reinforcers are used.

In oral ethanol self-administration studies, a common practice is to test single ethanol doses sequentially under continuous reinforcement schedules or under low FR schedules (Meisch, 1977, 1984). The present results demonstrate, however, that the drug dose that maintains the highest rate of responding under these conditions is not necessarily the dose that is least perturbed by increases in response demands (Experiment 1), nor is it the dose that is selected when two different doses are available concurrently (Experiment 2). It appears that, when the different doses are tested sequentially, response rate is not always a reliable index of the relative reinforcing effects of different doses of alcohol. Thus, caution is indicated when interpreting experimentally induced changes in the response rate maintained by a drug under these conditions in terms of changes in the reinforcing effects of the drug.

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