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CHLORDIAZEPOXIDE EFFECTS ON ETHANOL SELF-ADMINISTRATION: DEPENDENCE ON CONCURRENT CONDITIONS

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Experiments examined the effects of acute doses of chlordiazepoxide upon ethanol self-administration in the rat. A concurrent-schedule procedure was used that employed choice between ethanol (5%) and a second fluid (either water or a 1% sucrose solution). When ethanol and water were the available fluids, chlordiazepoxide at doses of 15 and 20 mg/kg reduced ethanol-reinforced responding and intake, with a greater reduction occurring at the 20 mg/kg dose. However, when ethanol and sucrose were concurrently available, in many rats only the 20 mg/kg dose of chlordiazepoxide reduced ethanol-reinforced responding. The differences in dose response function occurred in most animals without large changes in the baseline ethanol-reinforced responding across the two concurrent conditions. Thus the dose-effect curve relating chlordiazepoxide and ethanol self-administration can be altered, dependent upon the nature of the concurrently available reinforcers.

Key words: ethanol self-administration, chlordiazepoxide, concurrent schedules, economic analysis, fixed ratio, rate dependency, lever press, rats

The benzodiazapines interact with ethanol in a variety of ways in humans (Cushman & Benzer, 1980; Sellars & Busto, 1982). The most common effect is the enhanced sedative potency of alcohol when taken in combination with this class of drugs (Kissin, 1974). There is growing evidence that simultaneous abuse of alcohol and the benzodiazepines is extensive (Carroll, Malloy, & Kendrick, 1977; Cushman & Benzer, 1980; Freed, 1973). Because many of the pharmacological actions of the benzodiazepines are similar to those of ethanol, their use/abuse with ethanol may be an instance of drug substitutiton (Sellars & Busto, 1982). However, many cases of overdose in persons using these drugs have been reported, suggesting that in some cases reduction of ethanol intake failed to occur following benzodiazepine use (Tallman, Paul, Skolnick, & Gallager, 1980). Little is known of the possible environmental influences that may regulate drug self-administration when two pharmacologically interactive substances are involved.

The benzodiazepines are known to affect food and water intake (Cooper, 1983a, 1983b; Dantzer, 1977), and one effect, the dipsogenic action of the benzodiazepines, could result in increased ethanol intake. In a study of schedule-induced drinking, chlordiazepoxide (CDP) was found to increase both water and ethanol intakes in the squirrel monkey (Barrett & Weinberg, 1975). However, in mice, CDP administration either decreased or had no effect upon ethanol consumption in a variety of experimental conditions (Chan, Leong, & Schanley, 1983; Chan, Schanley, & Leong, 1983). With rats drinking ethanol on a schedule-induction regimen, chronic administration of CDP resulted in decreased ethanol intake (Roehrs, Yang, & Samson, 1984). One major difference between the rodent and monkey studies was that in the experiments with monkeys, the baseline levels of ethanol intake

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were low; but in the experiments with rats and mice, the baseline levels were close to metabolic capacity. Thus, increases in ethanol intake for the rodents would have resulted in very high blood ethanol levels.

Over the last several years, we have been using a concurrent-schedule procedure to examine oral ethanol self-administration (Roehrs & Samson, 1981, 1982; Samson, Roehrs, & Tolliver, 1982; Samson, Tolliver, & Roehrs, 1983). On this procedure, rats respond on a schedule of ethanol presentation in preference to responding on a concurrently available schedule of water delivery, and drink quantities of ethanol that result in pharmacologically significant blood ethanol levels. In these experiments, a unique differential response pattern was observed: When ethanol and water were concurrently available, very low rates of water-reinforced responding occurred (usually between 80 and 95% of total session responding was on the lever that produced ethanol). When 1% sucrose was the solution concurrently available with ethanol, total session responding increased, such that approximately equal amounts of lever pressing were maintained by the two schedules (i.e., ethanol-reinforced responding was about 50% of total responding), with little change, however, in absolute levels of ethanol-reinforced responding (Samson et al., 1982). These two concurrent conditions (ethanol-water and ethanol-sucrose) present an opportunity to observe the effects of acute benzodiazapine administration on different levels of total responding, while maintaining the same approximate absolute level of ethanol-reinforced responding. By comparing response patterns on the two concurrent conditions, it is possible to assess whether differential effects of acute benzodiazapine administration on ethanol self-administration depend upon the existing behavioral conditions.

METHOD

Subjects

Eight experimentally naive, adult male rats (Long-Evans strain), obtained from the breeding colony of the Psychology Department of the University of Washington, were housed individually in hanging stainless steel rodent cages in a multiple cage rack. Food and water were provided as described below. Artificial lighting was provided from 7:30 to 19:30 daily. Temperature and humidity were regulated as specified in the NIH animal guide (DHEW Publication [NIH] #78-23, 1978).

Apparatus

Four operant chambers, the same as those previously described (Roehrs & Samson, 1981), were controlled by appropriate interfacing with Apple computers. Each chamber could be equipped with two levers mounted on the front panel. These levers were removable as conditions dictated. To the outer side of each lever was an opening for delivery of a liquid dipper. Each dipper provided access to 0.1 ml of fluid when it was in the raised position. At each operation, the dippers remained in the access position for 3 s. The dipper located to the outside of each lever could be operated by responses on that lever. A houselight was illuminated during each session. The chambers were housed individually within sound-attenuating enclosures equipped with air-circulating fans.

Procedure

The initial procedures have been reported previously (Roehrs & Samson, 1981). These consisted of gradually reducing the animals to 80% of their ad-lib feeding weights by limiting their daily food ration. Following weight reduction, a 23 hr/day water-deprivation schedule was instituted.

Pressing the right lever was shaped first (with the left lever removed from the chamber), using water as the fluid presented in the dipper. When lever pressing was established, the response requirement was gradually increased over sessions to a fixed-ratio 8 (FR 8) schedule. When responding was stable, the right lever was removed and left-lever responding was shaped with water presented in the left dipper. When left-lever responding was stable under FR 8, water deprivation was discontinued. (Water was available at all times in the home cage for the rest of the experiment.) At this time, both levers were intro-

duced into the chamber, ethanol (5% V/V) was presented as consequence of responding on one lever and water was presented as consequence of responding on the other lever, with sides reversed each session. Also at this time in the procedure, 5 g of the animal's daily food ration was placed in the operant chamber prior to the start of each session. This procedure of placing food into the chamber was repeated for the next 7 to 10 sessions. The schedule was always concurrent FR 8 FR 8, with a 3-s changeover delay to decrease concurrent superstitious responding (Catania, 1966). When ethanol-reinforced responding became predominant (i.e., a majority of daily lever responses occurred on the lever that produced ethanol, such that responding followed the ethanol solution as its position alternated across sessions), the total food ration was given in the home cage following each session. All sessions lasted 30 min.

After the initial procedures were completed, the rats were exposed to 20 sessions with ethanol and water as the two reinforcers. As before, the assignment of solutions to levers changed each session. Following these baseline sessions, the rats were divided into two groups. Four of the animals remained in the ethanol-water condition, while for the remaining 4 rats, sucrose (1% W/V) was substituted for water. This specific ethanol-sucrose condition had previously resulted in approximately equal responding on both levers during each session without significant changes in absolute ethanol-reinforced responding (Samson et al., 1982). An additional 10 sessions were conducted for both groups to establish baselines for the ethanol-sucrose conditions.

After this second baseline was recorded, the effects of doses of CDP were studied using the following injection procedure. On Monday and Friday of each week, the animals received no injection prior to the daily 30-min session. On Tuesday and Thursday, an injection of isotonic saline was given in a volume equal to that of the drug dosage to be used that week. The injections were given 30 min prior to the start of the session. On Wednesday, the animals received either a saline or CDP injection. Chlordiazepoxide HCl (Hoffmann-La Roche) was dissolved in isotonic sterile saline immediately prior to injection. Doses of 10, 15, and 20 mg/kg CDP were tested. Each animal was tested at least twice at each dose.

After the determination of the dose-effect curve, the alternative solution was switched for the two groups: The ethanol-water paired animals were changed to the ethanol-sucrose condition and the ethanol-sucrose condition animals were returned to the original ethanol-water concurrent condition. After another 10-session baseline under these changed conditions, the animals were retested with additional doses of CDP using the same administration procedure as before. For all sessions following the stabilization of ethanol-water responding at the beginning of the experiment, daily records were obtained of total responding, total reinforcers presented, actual fluid consumed, and cumulative responding.

RESULTS

Mean numbers of responses for the 10 baseline sessions prior to drug administration for each concurrent condition are presented in Table 1. Percentages of total responding on the side with ethanol, and g ethanol/kg body weight intake are also presented. The calculation of percentage of total responding has been used in our prior work to indicate the relative reinforcing status of the available fluids (Roehrs & Samson, 1981). One subject (Rat 37) failed to develop preferential responding for ethanol in the water-ethanol concurrent condition. This rat had low overall response levels compared to the other rats in this condition, but when switched to the ethanol-sucrose concurrent condition, ethanol-reinforced responding increased by over 280%, with ethanol intake levels similar to those of the other rats. Because of the low responding in the ethanol-water condition, this rat's data were excluded from the statistical analysis for that condition. It should be noted that Rats 30 through 33 were placed in the ethanol-sucrose concurrent condition for the initial CDP testing and were then returned to the ethanol-water concurrent condition for determination of the second CDP dose-effect relation. The

Table 1
Baseline Response and Intake Levels

Ethanol-Water Condition					
Rat	*Ethanol*	*Responding Water*	*Total*	*% Ethanol/Total*	*Ethanol Intake (g/kg)*
30	558	60	618	88.6	1.11
31	259	93	352	72.8	0.52
32	209	69	278	74.3	0.44
33	535	71	606	88.2	1.24
36	395	175	570	68.4	0.75
37	97	90	187	50.6	0.18
38	301	116	417	70.6	0.58
39	718	76	794	90.4	1.49
Ethanol-Sucrose Condition					
Rat	*Ethanol*	*Responding Sucrose*	*Total*	*% Ethanol/Total*	*Ethanol Intake (g/kg)*
30	346	372	718	48.2	0.69
31	194	180	374	49.2	0.39
32	209	160	369	56.1	0.44
33	307	430	737	43.1	0.71
36	336	436	802	42.1	0.64
37	280	256	536	52.6	0.53
38	371	416	787	47.8	0.72
39	195	914	1109	17.7	0.40

remaining rats (36 through 39) were tested in the opposite order. The water-ethanol and sucrose-ethanol baseline data were taken from the week prior to CDP testing in each condition.

Statistical analysis for all rats (paired t test) comparing absolute total session baseline ethanol responding in the ethanol-water condition with absolute total session baseline ethanol responding at the initial stabilization of the ethanol-sucrose condition although approaching statistical significance [$t(6) = 1.782$; $p > .05$], was not statistically different. Individually, 2 rats had higher absolute amounts of ethanol-reinforced responding during the sucrose-ethanol pairing than during the water-ethanol pairing (Rat 37 discussed above and Rat 38; see Table 1). One rat showed little change between the two different pairing conditions (Rat 32), and 5 rats showed decreased ethanol-reinforced responding in the sucrose-ethanol condition when compared to their ethanol-reinforced responding in the water-ethanol condition (Rats 30, 31, 33, 36, and 39).

All rats showed marked increases in responding on the nonethanol side in the sucrose-ethanol condition as compared to the water-ethanol condition [$t(7) = 3.6158$; $p < .01$]. Because of the increases in sucrose-reinforced responding without significant decreases in ethanol-reinforced responding, total responding was also significantly greater in the ethanol-sucrose condition than in the ethanol-water pairing [$t(7) = 4.2826$; $p < .01$]. The ratio of ethanol-reinforced responding to total responding clearly reflects the changes indicated above (Table 1). In the ethanol-water condition, the mean ratio for ethanol was 79% of total responding (range: 68.4% to 90.4%, excluding Rat 37 as discussed above). These results are consistent with our previously reported data using these two concurrent conditions (Samson et al., 1982).

Table 1 also presents the average daily ethanol intake in g ethanol/kg body weight. During the ethanol-water condition, the average intake was 0.79 g/kg (± 0.45); in the ethanol-sucrose condition, a mean ethanol intake of 0.57 g/kg (±0.14) was found. This decrease as measured by ethanol ingestion was found to just reach statistical significance [$t(6) = 1.943$; $p < .05$]. This mean decrease was due primarily to those rats that showed high rates of sucrose-reinforced responding.

For example, Rat 39 had a marked increase in sucrose-reinforced responding that resulted in a decrease in ethanol-reinforced responding. Thus, although the mean decrease in absolute rate of responding on the ethanol lever failed to reach statistical significance between the two conditions, mean ethanol intakes were significantly decreased in the ethanol-sucrose condition relative to the ethanol-water condition. Although intakes are directly related to amount of responding, the intake in terms of body weight apparently altered the relation of change between the two conditions enough to result in statistical significance. However, caution must be used when using the mean data, for individual animals clearly showed opposite patterns of behavior in the two conditions.

In prior studies in our laboratory (Roehrs & Samson, 1981), ethanol intakes over 0.4 g/kg in 30 min resulted in blood ethanol levels of 50 mg/dl and greater. Although no blood ethanol levels were measured in the present experiment, the ethanol intakes observed were clearly sufficient to result in doses of ethanol capable of pharmacological interaction with behavior. Intakes were decreased in the ethanol-sucrose conditions, but they remained at levels that would be sufficient to produce pharmacological effects.

Individual dose-response curves for ethanol-reinforced responding in the two concurrent conditions are presented in Figure 1. Four rats (30, 31, 33, and 39) showed dose-related decreases in ethanol-reinforced responding in the ethanol-water condition and no clear relation in the ethanol-sucrose concurrent condition. Two rats (37 and 38) showed similar dose-related changes in both concurrent conditions, with less decreases in responding with CDP in the ethanol-sucrose condition. Rat 36 showed a clear dose relation, with responding decreasing as dose increased, but there were no differences in the dose-response curves generated in the two concurrent conditions. The effects of injections were found to be highly variable in Rat 32, with no clear relation between dose and conditions. Saline injections produced no systematic effects upon responding.

In order to examine statistically the major effects of dose upon responding, a comparison

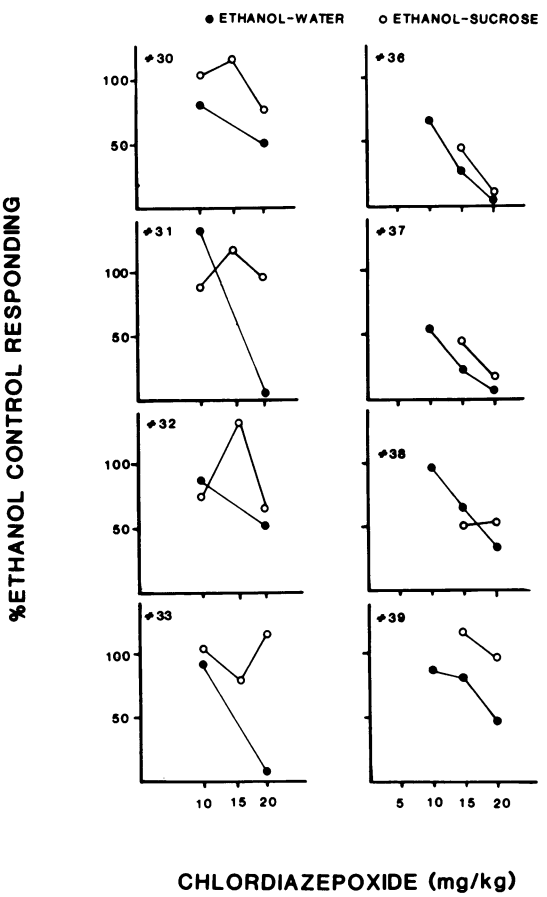

Fig. 1. Effects of saline and CDP administration on ethanol-reinforced responding expressed as percent baseline (y axis). Data are shown for all rats in the experiment. Unfilled circles represent effects of saline control injections and filled circles those of CDP (doses on x axis). Each point represents the mean of two determinations.

of responding on saline-injection days with drug days was performed using a paired sample post-hoc analysis. In the water-ethanol condition, significant decreases in ethanol-reinforced responding were observed at the 15 mg/kg CDP dose [$t(5) = 4.861$; $p < .01$] and the 20 mg/kg CDP dose [$t(15) = 5.436$, $p < .01$]. There were no statistically significant changes from baseline ethanol-reinforced responding for the 10 mg/kg CDP dose, but Rat 37 individually showed a decrease at this dose. Water-reinforced responding in this condition was not significantly changed from baseline except at the highest dose (20 mg/kg), at

Table 2
Mean ethanol intakes (g/kg) on saline (S) and drug (D) test days.

	Dose					
	10		15		20	
Rat	S	D	S	D	S	D
Ethanol-Water Condition						
30	1.26	0.93	—	—	1.11	0.51
31	0.60	0.82	—	—	0.51	0.00
32	0.49	0.56	—	—	0.44	0.17
33	1.32	1.01	—	—	1.33	0.00
36	0.42	0.34	0.69	0.21	0.68	0.02
37	0.17	0.09	0.16	0.06	0.24	0.02
38	0.54	0.54	0.70	0.46	0.59	0.19
39	1.32	1.24	1.55	1.20	1.48	0.77
Ethanol-Sucrose Condition						
30	0.64	0.64	0.60	0.67	0.80	0.60
31	0.63	0.66	0.61	0.73	0.54	0.54
32	0.45	0.21	0.45	0.49	0.42	0.28
33	0.68	0.63	0.54	0.37	0.66	0.74
36	—	—	0.63	0.21	0.56	0.05
37	—	—	0.49	0.23	0.53	0.19
38	—	—	0.70	0.36	0.73	0.35
39	—	—	0.42	0.65	0.38	0.39

All doses are mg/kg.

which there were significant decreases [$t(15) = 2.168$; $p < .05$]. It is important to point out that rather small absolute changes in water-reinforced responding could result in large relative changes (i.e., a decrease to 8 responses from 16 represents a 50% decrease but only a difference in one fluid delivery). Thus, it is not clear whether this statistically significant decrease represents a meaningful effect on water intake.

In the sucrose-ethanol condition, no statistically significant effects on ethanol-reinforced responding were found at either the 10 or 15 mg/kg CDP dose, but individually Rats 36, 37, and 38 showed decreased responding at the 15 mg/kg dose. At the 20 mg/kg CDP dose, a significant reduction in ethanol-reinforced responding was observed [$t(15) = 2.407$; $p < .05$]. Although there were decreases in sucrose-reinforced responding observed in some rats at some doses, no overall statistically significant effect of any CDP dose was observed.

An analysis of variance of the ethanol intake (g/kg) revealed that, as for ethanol-reinforced responding, statistically significant decreases in ethanol intake occurred at the 15 and 20 mg/kg CDP dose with the water-ethanol concurrent schedule, and at the 20 mg/kg CDP dose in the sucrose-ethanol pairing (Table 2). However, there were individual rats that clearly did not show this decrease.

To determine general CDP dose effects, an analysis of variance using a within-subjects design and repeated measures was employed. Before combining the data from both groups, an analysis was performed to assess whether the order of CDP testing had any significant effect. One significant difference was found: The rats that were first tested on CDP in the sucrose-ethanol condition (Rats 30 through 33) showed less suppression of ethanol-reinforced responding (10% decrease) in this condition at the 20 mg/kg CDP dose than did the rats that were retested with CDP in this condition (47% decrease). At all other doses and conditions, no significant differences in ethanol-reinforced responding were found.

Because, for the most part, there were no significant differences between the two groups of rats on the basis of the order of testing, the data were combined and a mean dose-effect curve for CDP in each condition was determined. Data were expressed as the percentage responding of drug days to saline injection days (Figure 2). The main effect for dose was found to be significant [$F(2,71) = 8.25$; $p < .01$]. The main effect for the concurrent condition was also found to be significant [$F(1,71) = 4.41$; $p < .05$]. Thus, ethanol-reinforced responding was dependent upon both dose and the concurrent condition, with increased suppression of ethanol-reinforced responding typically occurring as dose increased and with greater suppressions found most often when ethanol was paired with water. This conclusion is supported by a significant interaction between dose level and condition [$F(2,71) = 5.62$; $p < .01$]. The effects of CDP on sucrose and water-reinforced responding were not similar (Figure 2). Little relation was apparent for sucrose and although water-reinforced responding was suppressed at both the 15 and 20 mg/kg doses, the degree of suppression was equal for both these doses.

Examination of the cumulative records sub-

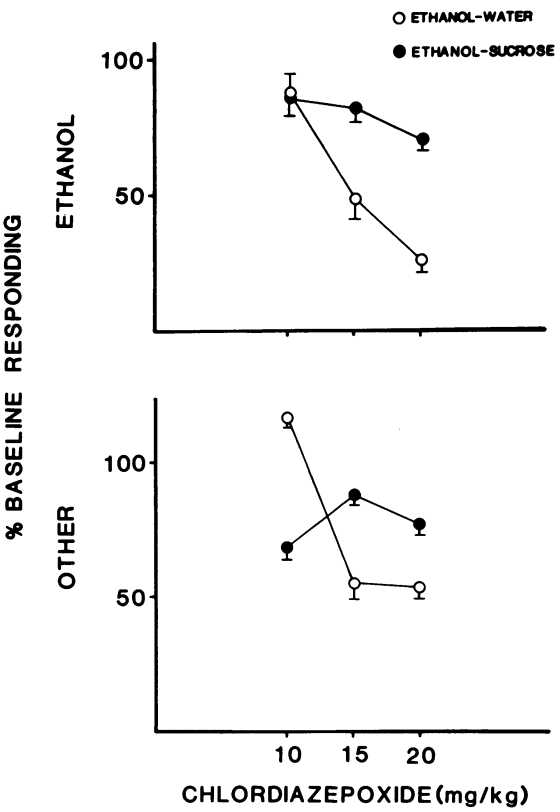

Fig. 2. Mean effects of CDP administration (x axis) on percentage of baseline responding reinforced with ethanol and with the alternative fluid (y axis) in each concurrent condition. (Error bar represents the SE_M; unfilled circles are for the ethanol-water condition; filled circles represent data in the ethanol-sucrose condition.)

stantiated the differential effects a given dose of CDP had dependent upon the concurrent pairing condition. Figure 3 presents a representative cumulative record at the 20 mg/kg dose for Rat 30. For this rat, CDP decreased ethanol-reinforced responding (48% decrease) and increased water-reinforced responding (68% increase) in the ethanol-water pairing. In the ethanol-sucrose pairing, the same dose of CDP decreased ethanol-reinforced responding by only 8% and made little difference in sucrose-reinforced responding (2% increase in the CDP session from saline baseline).

DISCUSSION

The effects of CDP upon ethanol self-administration were found to be dependent upon the experimental conditions in which the animal was tested. When ethanol and water were the alternatives, systematic decreases in ethanol-reinforced responding were found as CDP dose increased, with a marked reduction in responding occurring at the 20 mg/kg dose. However, when ethanol and sucrose were the alternatives, CDP was found generally to have less effect, and for several animals CDP injections reduced ethanol-reinforced responding only at the 20 mg/kg dose. This difference in CDP efficacy between the two concurrent conditions was not due to major changes in ethanol intake; for most rats it remained consistent and independent of the concurrently available alternate fluid. No systematically increased ethanol-reinforced responding was observed in any condition, suggesting that the dipsogenic effects of CDP reported by other investigators (Cooper, 1983a, 1983b; Cooper & Francis, 1979; Dantzer, 1977) did not increase ethanol self-administration. An increase in water-reinforced responding did occur at the 10 mg/kg CDP dose for several animals, but this was not a statistically significant group effect. Additionally, it should be noted that rates of baseline water-reinforced responding were generally very low; hence these increases do not represent a very substantive increase in water intake.

Although there are no reported studies in rats that have examined the relation of CDP dose when ethanol is the only reinforcing stimulus presented, there are many studies that have used food reinforcement (for reviews, see Dantzer, 1977; Sanger & Blackman, 1981). Some investigators have observed increases in food-reinforced responding on FR schedules at low CDP doses (Wedeking, 1973, 1974), but others have either failed to find any increases or have found increases when using fixed-interval (FI) schedules but not when using FR schedules (Sanger & Blackman, 1976). At higher doses of CDP, decreases in food-reinforced responding have been shown, independent of the schedule of reinforcement (Sanger & Blackman, 1976, 1981). These decreases in food-reinforced responding are in contrast to observations of increased 24-hr food consumption with CDP administration in

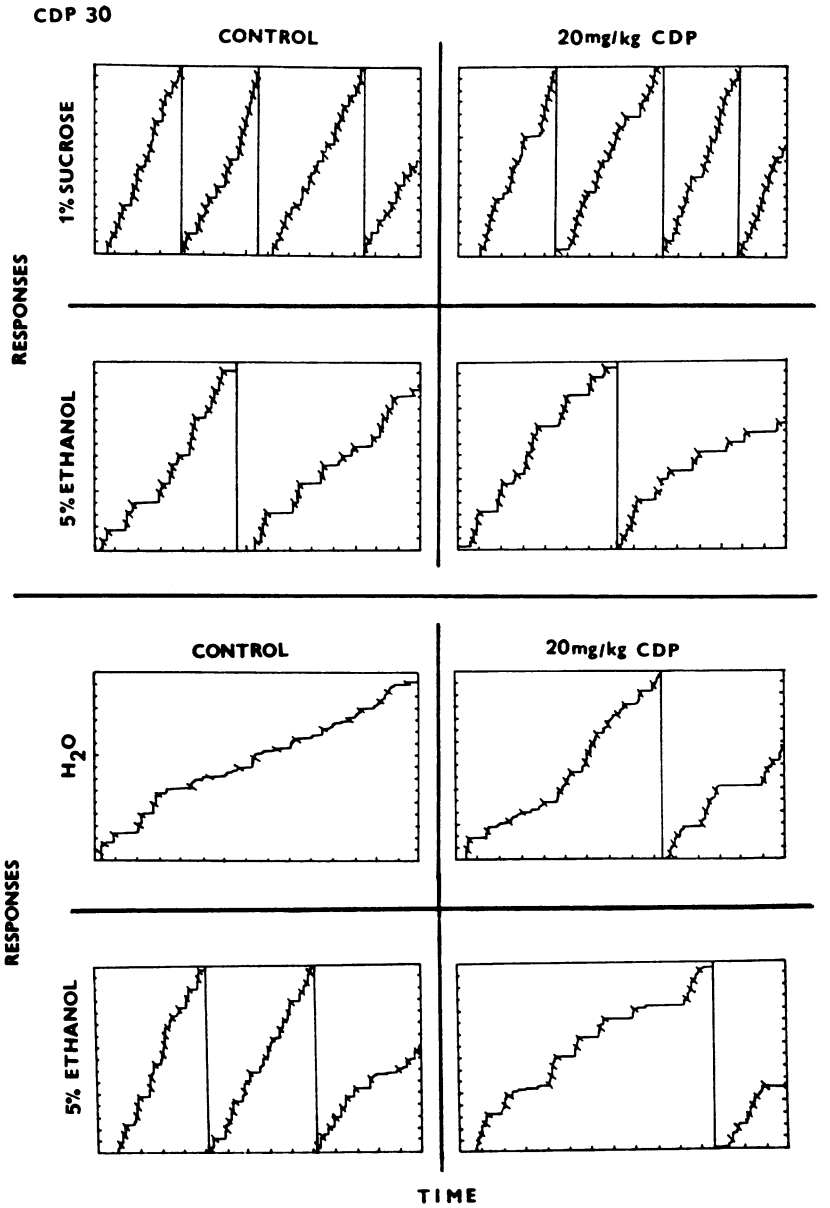

Fig. 3. Representative cumulative response records for Rat 30. Same-session records for both the ethanol and concurrently available reinforcer during saline (left panels) and 20 mg/kg CDP injection sessions (right panels) are shown. Cumulative responses are indicated on the y axis (one division = 10 responses) with time on the x axis (one division = 2 min). Slashes represent reinforcements.

both food-restricted and free-feeding rats (Cole, 1983; Dantzer, 1977).

Chlordiazepoxide has been shown to increase intakes of both water and ethanol in experimental conditions that result in schedule-induced polydipsia (Barrett & Weinberg, 1975). However, with CDP doses similar to those in the present study, but in chronic 24-hr schedule-induced drinking experiments, only decreased ethanol or water intakes were found (Roehrs et al., 1984). Since in the present studies no significant increases were found for responding reinforced by any of the available fluids at any dose tested, it would seem that the prior finding of Sanger & Blackman (1976) of dose-related decreases in responding maintained by a single reinforcer on FR schedules is comparable to the results found in these ex-

periments when two fluids were available concurrently. To explore the possibility that a lower dose of CDP might increase ethanol- or water-reinforced responding, 4 of the rats in the experiments reported here were studied with a single CDP injection of 5 mg/kg in the standard weekly procedure after the end of the experiment. No consistent changes in responding were observed.

To determine if the effects were rate dependent (Dews, 1981), a correlational analysis was performed. A comparison of the log percentage change in responding on the ethanol-correlated lever on drug days to log baseline response rate on saline days revealed no statistically significant relation at any CDP dose in either the ethanol-water or the ethanol-sucrose condition. Also, examination of the sums of ethanol and alternate fluid responding resulted in no significant correlations at any dose. The lack of a rate-dependency effect with CDP has been reported in other experimental conditions (Sanger & Blackman, 1981).

Laties (1971) also found that the concurrent availability of two reinforcers can result in different effects of a drug upon responding, as compared to the drug's effects upon responding when each reinforcer is individually presented. In that study, administration of amphetamine increased responding that was maintained by delivery of heat when that was the only available reinforcer, but decreased the heat-reinforced responding and increased food-reinforced responding when both were concurrently available. Laties suggested that in the concurrent condition the increased alternative (food-reinforced) behavior was incompatible with the heat-reinforced responding. Although that explanation could account for the data in Laties' experiment, the present experiment found no consistent increase in responding maintained by the alternative reinforcer when ethanol-reinforced responding was decreased. Thus, incompatible competing responses maintained by the alternative fluid fail to account for the results observed in the present experiments.

That a drug can affect responding differentially, dependent upon the experimental conditions, has been demonstrated previously in a variety of situations (McKearney, 1979). For example, in studies using both food- and shock-maintained behavior (Barrett, 1976, 1977), the effect of CDP on responding in a multiple schedule has been shown to decrease shock-reinforced responding while increasing food-reinforced responding. In the same experiment, cocaine was shown to increase both types of responding. Thus, changes in responding due to a given drug can result from an interaction between the reinforcers presented as well as from more direct effects of the drug itself. The same investigators have also shown that prior behavioral experiences can reverse the effects of some drugs upon responding in a given environmental situation (Barrett & Stanley, 1983; Glowa & Barrett, 1983). These findings are compatible with the effect reported here, and suggest that an interaction of concurrent conditions and the dose response relation is dependent upon many factors, of which the available reinforcers are but one.

Although there is a large body of literature on concurrent schedules, most of these studies have been concerned with the relations between schedules, and have predominantly used a single type of reinforcer (e.g., Baum, 1981; de Villiers, 1977; Herrnstein, 1970; Rachlin, 1978). Extensive comparison of this literature to the present study is therefore difficult, given our use of concurrently available, qualitatively different reinforcers. However, a study by Lea & Roper (1977) is relevant; they examined the effects of FR size and quality of food pellets on concurrent performance in rats. Using a micro-economic theory approach, they found that changes in responding related to FR requirements interacted with the quality of the alternatively available reinforcer. They suggested that reinforcer elasticity (for a review of the use of economic concepts, see Hursh, 1980) was predictive of the FR effect and that no simple rule, such as matching, could account for the choices they observed. Applied to our previous work (Samson et al., 1982), a similar economic analysis suggests that demand for ethanol reinforcement might decrease (increased elasticity) when sucrose is substituted for water as the concurrently available reinforcer. However, a complex economic demand function for eth-

anol was observed in the data showing an interaction of the FR schedule and the concentration of the alternative sucrose solution presented. Because the concentration of sucrose used in the present study did not greatly alter ethanol-reinforced responding from that observed when water was the alternately available reinforcer, the actual demand functions for ethanol appear little changed. Although it is possible that the demand function was different in the two concurrent conditions, and could account for the differential effect of CDP, only further studies that manipulate the reinforcement schedule in each concurrent condition can clarify the relation of reinforcer elasticity and drug effect.

Application of economic theory to the experimental analysis of behavior has suggested the use of FR schedules to assess reinforcer "cost" (Hursh, 1980). However, the major goal of the present studies was to explore oral ethanol self-administration rather than to determine reinforcer demand functions. Inasmuch as the effects of oral ingestion of a psychoactive substance are obviously dependent upon the rate of intake, the schedule used to determine self-administration should not greatly restrict the animal's capability to self-regulate that rate. The use of an FR schedule requiring few responses to obtain each unit of ethanol appears to meet this requirement. That these FR schedules may be appropriate for economic analysis is an additional benefit to be further explored.

Another explanation for the difference in drug effect with change in concurrent conditions is a possible difference in stimulus control. As external stimulus control increases, the effects of a given dose of drug have been shown to decrease (Laties, 1972; Laties, Wood, & Rees, 1981; Thompson, 1978). The reinforcing stimuli in the present concurrent condition are also discriminative stimuli (Michael, 1982; Schuster & Balster, 1977), which may exert different degrees of stimulus control over schedule-appropriate patterns of responding. If there is greater stimulus control in the ethanol-sucrose concurrent condition than in the condition with water concurrently available, then the observed results are in agreement with other studies on the effect of external stimulus control. However, to strongly support this interpretation, one would have to isolate the discriminative effects from other behavioral effects of adding sucrose to water.

Although no simple and direct extrapolations can be made from these data to human situations, there is a suggestion that ethanol intakes might not be reduced at times of added ingestion of benzodiazepines if the co-use occurred in environmental situations in which other reinforcers were concurrently available. This, of course, is frequently the case. Even though in some cases decreased ethanol intake would result from concurrent use of benzodiazepines, there could be situations in which no reduction in ethanol intake would occur. At these times, the potential for overdose would be increased. Only further work with humans can determine the role that concurrently available reinforcers may have upon dose-effect relations of drugs, but the data here suggest that these relations may be greatly different depending upon both the types and schedules of available reinforcing stimuli.

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