Pharmacology Biochemistry & Behavior, Vol. 34, pp. 855–861. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Parallel Development of Ethanol Tolerance and Operant Compensatory Behaviors in Rats[1]

FRANK A. HOLLOWAY[2] AND DAVID A. KING[3]

Department of Psychiatry and Behavioral Sciences, University of Oklahoma Health Sciences Center Oklahoma City, OK 73190-3000

Received 6 April 1989

HOLLOWAY, F. A. AND D. A. KING. *Parallel development of ethanol tolerance and operant compensatory behaviors in rats.* PHARMACOL BIOCHEM BEHAV **34**(4) 855–861, 1989.—This experiment was designed to detect compensatory learning that has been suggested to occur during the course of tolerance development to ethanol's effects on operant performance. The effects of presession ethanol injections on the development of tolerance to ethanol's effects on operant performance in an afternoon Fixed-Ratio (FR) task was assessed in rats that were concurrently performing in a morning DRL task. Only presession saline injections were administered for the DRL task. A cumulative dosing procedure was used to establish initial and postethanol exposure dose-effect curves for both tasks. Daily presession ethanol administration produced a 3-fold shift-to-the-right in the dose-effect curve for FR-task performance. No changes were evident in the FR-task performance of controls that received daily saline injections. However, during the period of daily ethanol injections and during subsequent cumulative dose tests, the ethanol, but not the control, group displayed dose-related increases in total DRL-task responses relative to baseline. These DRL data were interpreted as reflecting the development of rate-increasing behaviors that compensated for and contributed to the tolerance of ethanol's rate-decreasing effects on FR-task performance.

Ethanol Tolerance Operant performance Rats Cumulative dose-effect curves Drug-induced compensatory learning

THIS laboratory recently demonstrated the development and persistence of tolerance to ethanol's (ETOH) effects on rat operant performance. Significant shifts to the right in dose-effect curves for ETOH's rate-decreasing and/or rate-increasing effects on performance using fixed-ratio (2, 9, 10), variable interval (2), and differential reinforcement of low rates (DRL) (1) schedules of food reinforcement developed over the course of chronic ETOH exposure. Tolerance to these ETOH effects persisted up to six months, well past that usually reported for metabolic or physiological tolerance. We suggested these incidences of behavioral tolerance (9,10) were the result of some new instrumental compensatory behavior developing during episodes of intoxicated practice as a consequence of ETOH-induced disruption of the rats' ability to meet the reinforcement schedule requirements unique to the behavioral task.

If at least a portion of the ETOH tolerance effect reflected in operant performance depends on some learned compensation for the acute effects of ETOH, then what is learned should depend on the task demand characteristics. For example, in the Fixed-Ratio (FR) schedule (2,9) the principal acute effects of ETOH at moderate and high doses is a rate-decreasing one. If tolerance to this acute ETOH effect is learned, one might expect the learned compensatory response to be one that compensates for loss of reinforcements with some new rate-increasing strategy. If so, then such a learned reaction may depend on the response-demand characteristics of the task on which the animal has intoxicated practice and/or the contingency relationship between responses and reinforcements. Further, any learned tolerance effect involving a rate-increasing strategy would be most evident in a task sensitive to rate-increasing effects [e.g., a DRL operant task (1)].

In some ways, the hypothetical compensatory behavior thought to be acquired during task-related drug exposure is analogous to what Dickinson (5) described as "behaviorally silent learning," which can only be detected by looking for such changes in a different behavioral task. For example, the conditioned suppression effects of a tone paired with shock are easily demonstrated by examination of the behaviorally suppressive effects of the tone on appetitively motivated operant performance. In this light, the

[1]This research was supported by National Institute on Alcohol Abuse and Alcoholism grants 5 T32 AA07222 and 5 RO1 AA06351 to F. A. Holloway.
[2]Requests for reprints should be addressed to Frank A. Holloway, Ph.D., University of Oklahoma Health Sciences Center, Research Building, 306-R, P.O. Box 26901, Oklahoma City, OK 73190-3000.
[3]Present address: University of Vermont, Department of Psychology, Burlington, VT.

present study was designed to at least indirectly assess the nature of any compensatory response strategy that may accompany the development of ETOH tolerance. Rats were trained in daily double sessions on operant tasks with competing response requirements [i.e., DRL (morning) and FR (afternoon) tasks], but were given intoxicated (presession ETOH) practice only on the FR task. We hypothesized that if rats acquire tolerance to ETOH's rate-decreasing effects on FR performance by developing a rate-increasing strategy while intoxicated, then such an effect may be reflected in these rats' DRL performance.

METHOD

Subjects

Twelve male Sprague-Dawley rats (Sasco, Inc., Omaha, NE) were used as subjects. The rats weighed between 250–275 g at the beginning of each experiment. All animals were individually housed in standard stainless steel wire-mesh suspended cages with continuous access to water throughout all experiments. Animal care and maintenance were provided by the University of Oklahoma Health Sciences Center Department of Comparative Medicine, an AALAC-accredited humidity- and temperature-controlled facility. After a one-week acclimation period on ad lib food, rats were food-deprived and maintained at 85% of their free-feeding weights (325–415 g) by supplemental feeding in addition to food reinforcement earned during the experimental sessions. Target weights were allowed to increase gradually over the course of experiments (5% per month) to allow for normal growth. All rats were maintained on a 12-hour light/dark cycle, with behavioral sessions occurring during the light phase at the same time each day.

Behavioral Apparatus

Twelve identical operant chambers (Model 80001, Lafayette Instruments, Lafayette, IN) were used. These chambers contained a single response lever, stimulus and house light, food cup, and an exhaust fan [see (10)]. Environmental and behavioral contingencies were accomplished by interfacing the operant chambers (Rayfield Inc., Waitsfield, VT) with two Commodore-64 computer systems (one for each six operant chambers) that used a PROMAL-based software system (16).

Operant Training Procedures

After the initial food-deprivation procedures, rats were trained to the magazine food delivery system and to lever-press for continuous food reinforcement (FR-1) by the method of successive approximations. During this initial shaping procedure the stimulus and house lights were illuminated during each 30-minute session.

After the rats began responding reliably, Phase 1 of the training began. In this phase animals were trained twice daily under two distinct schedules of reinforcement. At 0800 hours all animals were trained to respond under a differential reinforcement of low rates, 15-second schedule (DRL-15s) that required a minimum of 15 seconds between responses for a reinforcer delivery.

An auditory signal (4.5 kHz, Sonalert), external to the operant chambers, was presented throughout this morning session. At 1230 hours all animals were trained to respond under a FR-30 schedule of food reinforcement. When all rats met the criterion performance of three consecutive days of a response-to-reinforcement ratio of less than four for the DRL task and no more than 20% variance in the number of reinforcers delivered during the FR task, Phase 2 of the training began. In Phase 2 training, a multiple Time-Out component was added [adapted after Wenger (21)] such that all sessions consisted of three cycles, each of which began with a 15-minute Time-Out period (no food reinforcement and stimulus and house lights off); each Time-Out period was followed by a 10-minute Time-In period (schedule-controlled food reinforcement and stimulus and house lights on). All sessions began with placing the rat into a darkened chamber. Performance on this final training phase was judged stable when response rates across cycles for four consecutive days varied less than $\pm 10\%$.

Ethanol Dose-Effect Curve Procedures

Once stable performance in both tasks were met, rats were divided into two groups (N = 6/group). Baseline performance was determined by intraperitoneal (IP) injection of saline alone in a volume equivalent to that of the corresponding ETOH dose that would be administered in subsequent ETOH cumulative dosing test sessions. Baseline performance for each cycle was the average of three saline baseline sessions. An initial dose-effect curve was determined in each subject using a cumulative injection regimen at the beginning of each session and of each Time-Out period. Three sequential ETOH doses (10% w/v solution with 0.9% saline vehicle) were administered by IP injections. The ETOH doses were: 0.5, 0.75, and 0.75 g/kg, which provided cumulative doses of 0.5, 1.25, and 2.0 g/kg. Note that the interval between injections and the next Time-In period was always 15 minutes and the interinjection interval was always 25 minutes (i.e., the Time-Out plus the Time-In intervals). Pilot studies with an FR30 operant task indicated equivalent ETOH dose-effect curves and ED_{50} values using either the cumulative dosing regimen just described or the more traditional single dosing regimen used earlier (2).

Dose-effect curves were obtained for the FR task session first, then 48 hours later for the DRL task. Once these initial dose-effect curves (PRE) were obtained for both operant tasks, half of the animals received four weeks of presession ETOH injections prior to the FR task (ETOH group), while the other half received an equivalent volume of saline (CONTROL group). The ETOH dose was increased over the four-week period (1.25 g/kg on Week 1, 1.5 g/kg on Week 2, and 1.75 g/kg on Weeks 3 and 4). One day after the last day of the chronic ETOH regimen, dose-effect curves were redetermined for the FR task, and were redetermined for the DRL task two days later (POST-1). One month later a third dose-effect curve was redetermined in both tasks in a similar fashion (POST-2). Normally scheduled DRL and FR sessions continued during days between all ETOH dose tests on the FR and DRL tasks and during the one-month interval between the POST-1 and POST-2 test series. Finally, two months after the POST-2 test, baseline performance for the DRL task only was reestablished in the CONTROLS. The rats then were given a cumulative dose test, followed by three weeks of presession ETOH injections (1.25, 1.5 and 2.0 g/kg on successive weeks) and by a final cumulative dose test.

Breath Ethanol Assay

Breath ETOH samples were obtained using a procedure adapted from Pohorecky and Brick (15) [see also (10,20)]. The samples were assayed by a gas chromatographic (GC) method similar to that used by others (9,17). Briefly, rats were placed in a sealed desiccator jar 15 minutes after each of the cumulative ETOH injections used for the behavioral dose-effect tests. They were left in the jar for seven minutes. A 1-ml air sample was withdrawn through the jar septum with a gas-tight syringe and injected

TABLE 1

BASELINE PERFORMANCE FOR ETOH AND CONTROL GROUPS (MEANS/STANDARD ERRORS)

Task	Group	Measure	Cycle-1	Cycle-2	Cycle-3
FR30	ETOH	Tot-Resp	830/123	868/202	832/120
		(Reinf.)	(27.7)	(28.9)	(27.7)
	CONT	Tot-Resp	757/107	749/1125	760/135
		(Reinf.)	(25.2)	(24.9)	(25.3)
DRL15	ETOH	Tot-Resp	46/4	44/5	43/6
		(Reinf.)	21/3	20/2	22/2
	CONT	Tot-Resp	52/6	51/5	48/7
		(Reinf.)	17/2	15/2	17/3

directly into the GC (Hewlett-Packard 5890) port [for system parameters, see (10)]. The index of ethanol levels (mg%) were obtained by linear regression for area under the curve for samples against that for standards. The cumulative dose-effect curves for breath ETOH levels were obtained one day after the first and second DRL task cumulative dose tests.

Data Analysis

Analyses of variance (ANOVA) were employed to examine the main effects of cumulative dose tests and ETOH dose on total responses (expressed as % total baseline responses for that cycle; e.g., Cycle-1 for the 0.5 g/kg dose, etc.) of each group on the FR and DRL tasks. A similar analysis was used for the mg% ETOH data. ED_{50}s for dose-related reduction in % baseline responses on the FR task were calculated by a linear regression analysis. A three-way ANOVA was performed on % baseline responses during the four-week daily injection periods [Weeks (dose) × Task × Group]. Separate ANOVAs were performed on DRL reinforced and nonreinforced responses (expressed as a % of total responses) from each group and test (Baseline, PRE, Post-1, Post-2) condition.

RESULTS

Breath Ethanol Levels

While both groups displayed dose-related increases in breath ETOH levels on the PRE and POST-1 tests, no significant group differences on either test were found and no significant PRE vs. POST-1 differences were found at any dose or for either group. Overall, the range of mean ETOH levels of each test doses were: 0.5 g/kg: 61–71 mg%; 1.25 g/kg: 105–119 mg%; and 2.0 g/kg: 147–160 mg%.

Baseline Operant Performance

Table 1 shows the saline baseline performance for both groups, both operant tasks, and each cycle. These data represent averages over two sessions given the week prior to the PRE test. No group differences were found for either task on any measure. However, the ETOH group's overall DRL performance as indexed by % reinforced response was marginally higher ($p<0.10$) than that for the control group [mean (ETOH) = 44%; mean (CONT) = 32.5%]. For this reason, all other performance analyses were performed on data expressed as % Baseline at each cycle.

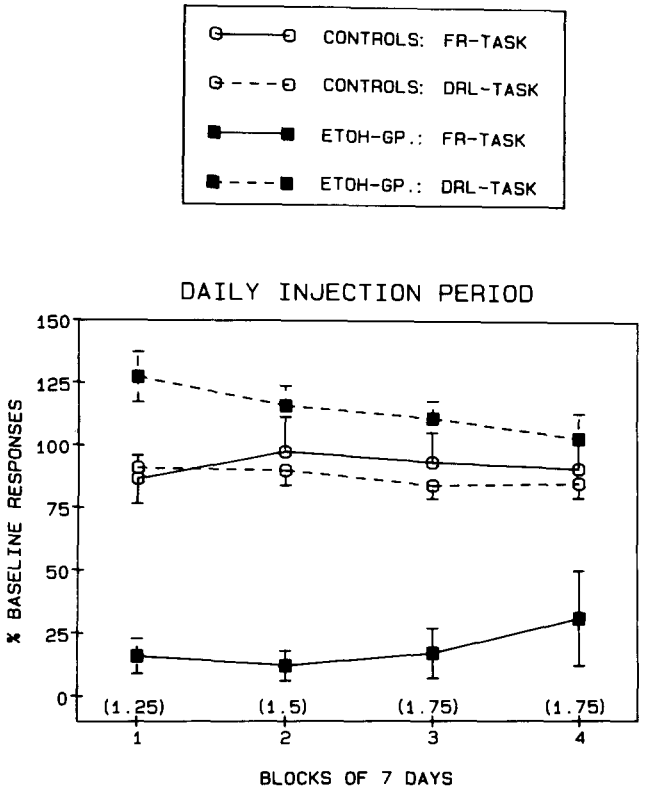

FIG. 1. Percent of saline baseline total responses during period of daily injections (means and S.E.s). The presession ethanol doses (in g/kg) for the ETOH group's FR-task data are given in the parentheses.

Responding During Daily Injection Period

Figure 1 illustrates responding in each task by each group over the four-week injection period. Overall, the ETOH group displayed significantly less responding on the FR task than did the controls ($p<0.01$). This finding was expected since the ETOH group received presession ETOH injections. Also apparent was significantly greater responses by the ETOH group relative to CONTROLS on the DRL task (overall, $p<0.05$). This effect was significant (p's<0.05) on all weeks except the last one ($p<0.10$).

ETOH Cumulative Dose Tests for the FR Task

Figure 2 (A,B) presents the data for % baseline responses at each cumulative dose test. The ETOH and CONTROL groups did not differ on the initial (PRE) test for either task or on any ETOH dose. Both groups displayed monotonic dose-related decreases in responding on both tasks, unlike the biphasic curves for DRL performance reported by Bird and Holloway [(1), but see below]. However, on the first postchronic injection test for the FR task, the ETOH group displayed significantly greater responding than the CONTROL group at the 0.5 g/kg ($p<0.05$) and the 1.25 and 2.0 g/kg test doses (p's<0.01). This latter effect was still evident in the ETOH group's performance on the last FR dose-effect test ($p<0.01$) with the 1.25 g/kg dose. The ETOH group, but not the CONTROL group, also displayed a significant tolerance develop-

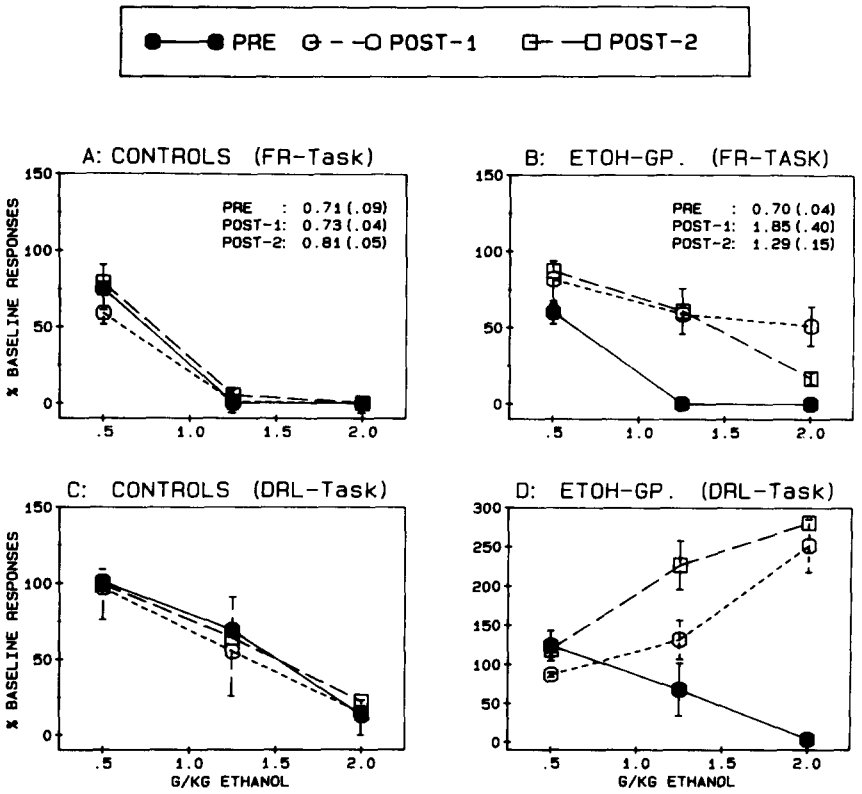

FIG. 2. Percent of saline baseline total responses at each ethanol cumulative dose test (means and S.E.s). The ED_{50}s for ethanol's rate-decreasing effects on FR-Task performance are indicated (mean and S.E. in g/kg).

ment to ETOH's rate-decreasing effects, indicated by a shift to the right in their postchronic period dose-effect curves. Both POST-1 and POST-2 tests for the ETOH group generated greater responding at each test dose (all p's<0.05) and higher ED_{50}s (p's<0.05) than did the PRE test. However, some tolerance loss was evident on the POST-2 test (relative to POST-1), where less responding at the 2.0 g/kg dose and lower ED_{50} values were found (p's<0.05). The CONTROL group displayed no such changes in % baseline responses or ED_{50}s across test sessions.

ETOH Cumulative Dose Test for the DRL Task

Figure 2 (C,D) also illustrates performance on the DRL task at each cumulative dose test. The CONTROL group displayed no reliable changes in responding across tests and did not differ from the ETOH group on the initial (PRE) test. However, on the POST-1 and POST-2 tests at the 1.25 and 2.0 g/kg doses, the ETOH group displayed significantly higher % baseline responses relative to both their PRE tests (p's<0.01) and to the CONTROLS on the POST-1 and POST-2 tests.

Although the ETOH group displayed a significantly higher number of reinforced and nonreinforced responses (p's<0.05) on the POST-1 and POST-2 tests at the 1.25 and 2.0 g/kg doses (relative to saline baseline reinforced and nonreinforced responses), these data (not shown) do not entirely reflect the pattern of DRL performance. Figure 3 illustrates the interresponse time (IRT) distributions (averaged across all ETOH test doses) for each group. Note these data represent percent of total responses on each test (the baseline distribution is included for comparison). Figure 3 shows that: (a) the ETOH group's performance on the PRE test was somewhat better than that of the CONTROL group (i.e., proportionately more reinforced responses); (b) both groups displayed a shift toward shorter IRTs on the initial (PRE) test; (c) the ETOH group displayed an even larger shift to shorter IRTs on the POST-1 and POST-2 tests, particularly at the two higher doses; but (d) the CONTROL groups' IRT distribution was relatively constant across cumulative dose tests. At the two higher doses, the ETOH rats displayed proportionately faster rates of responding at the POST-1 and POST-2 tests than were evident on their initial PRE test or in comparisons to that of CONTROLS on the POST-1 and POST-2 test (all p's<0.05). Further, a significantly smaller percent of the ETOH group's total responses on the POST-1 and POST-2 tests at the two higher doses were reinforced (relative both to their PRE or baseline performance and to the performance of the CONTROLS on the POST-2 and POST-2 tests, all p's<0.05). More generally, the postchronic pattern of IRT's for the ETOH group suggests that this group's DRL behavior was less adaptive (i.e., resulted in relatively fewer reinforcements) than was the case on their initial dose test.

FR/DRL Task Interactions

The initial PRE dose-effect curves for the ETOH and CONTROL groups indicated only dose-related decreases in DRL-task responding, unlike the biphasic dose-effect curves reported by Bird and Holloway (1). Thus, in order to determine whether the concurrent presence of the FR task may have influenced the form of these curves for DRL responding, the CONTROLS were given three weeks of intoxicated practice on the DRL task alone. On their initial cumulative dose test, this group displayed significant

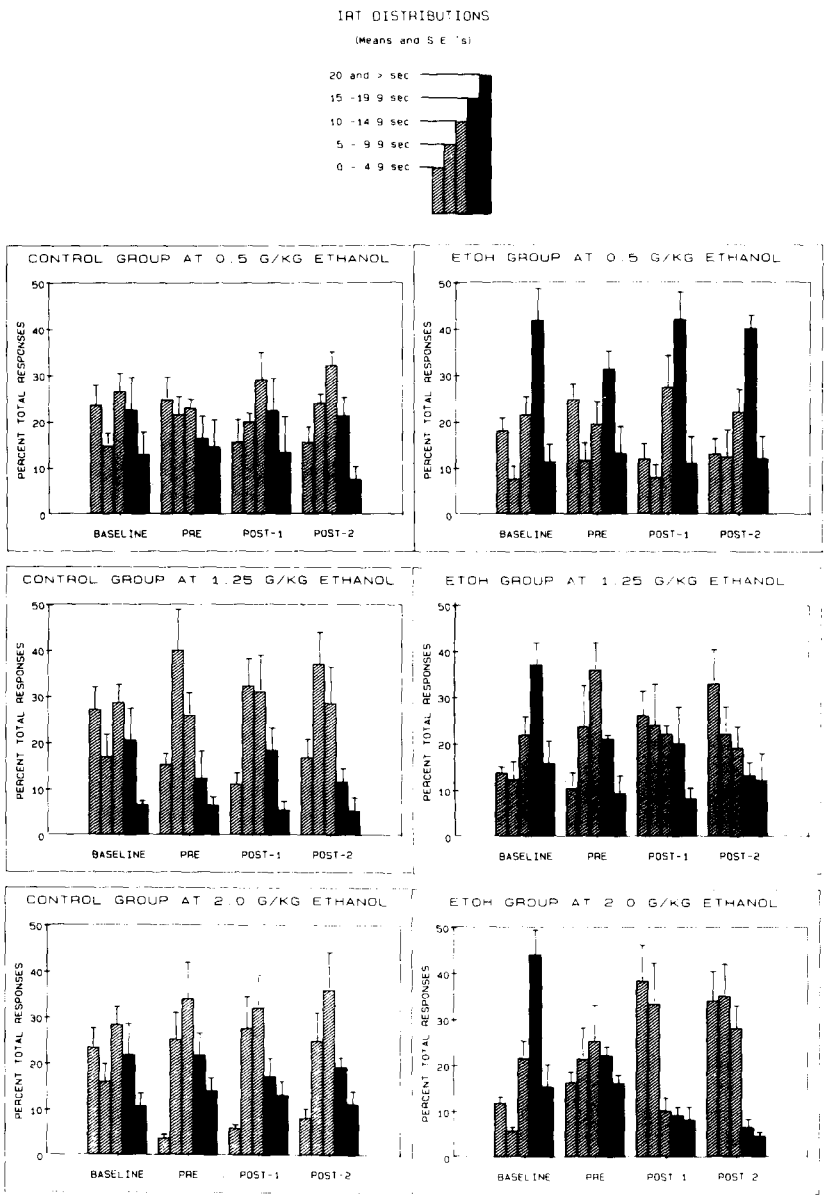

FIG. 3. The interresponse time (IRT) distributions for CONTROL and ETOH groups at each ethanol dose and cumulative dose test. Note that the baseline data represent data from cumulative saline injections prior to each session cycle on that day.

increases ($p<0.05$) in % baseline responses at the 0.5 g/kg dose (0.5 g/kg: mean = 115.3%, S.E. = 4.5%; 1.25 g/kg: mean = 98.3%, S.E. = 2.9%; 2.0 g/kg: mean = 52.0%, S.E. = 12.9%). This group also displayed a shift to the right for this rate-increasing effect on their final test (0.5 g/kg: mean = 107%, S.E. = 11.1%; 1.25 g/kg: mean = 154.0%, S.E. = 12.2%; 2.0 g/kg: mean = 88.2%, S.E. = 11.1%). On this final test, responding at the 0.5 g/kg dose no longer differed from baseline, but the two higher doses produced significantly higher % baseline responses relative to the initial test (p's<0.01). It is noteworthy that even the final dose-effect curve was biphasic, unlike the monotonic increasing dose-effect curve seen for ETOH group's DRL performance at the POST-1 and POST-2 tests. Thus, the concurrent performance of the FR and DRL tasks appeared to have altered the initial ethanol dose-effect function for DRL performance by eliminating rate-increasing effects of lower doses.

DISCUSSION

Several investigators (4, 7, 8, 11) have argued that, in general, tolerance develops to a drug's effects on behavior and not to the drug itself. Goudie and colleagues (4, 7, 8) further suggest that whenever a drug produces a behavioral change that results in reinforcement loss, some coping or compensatory behavior comes into play. Prior investigations from this laboratory (1, 2, 9) have suggested that much of the tolerance to ethanol's effects on operant performance derives from the animal's ability to learn some as yet undefined compensatory behavior that counteracts ethanol's disruptive effects and consequent reduction in reinforcement density. Such decreases in reinforcement density set the

occasion for some behavioral adjustment or change (7,18). This hypothesis implies that tolerance can occur to ethanol-induced performance impairment resulting either from rate-decreasing or rate-increasing effects.

The current study suggests the nature of any learned compensatory effect acquired through intoxicated practice may be specifically related to the particular requirements of the task and to the nature of the ethanol-induced disruption of performance (rather than to some nonspecific ethanol effect), a view similar to that expressed by Chen (3). Such task-specific tolerance effects have been previously reported for amphetamine [see (6,22)]. However, as Goudie points out (7,8), the coping strategies thought to be mediated by instrumental learning are as yet hypothetical entities. The experimental design of this present study appears to address this issue. In the FR operant task (where the primary ethanol effect is a rate-decreasing one), the hypothetical compensatory strategy would be a rate-increasing one. By utilizing a concurrent DRL task earlier in the day, we had hoped to track the development of such a compensatory strategy, predicting that ethanol-induced rate-increasing effects would be evident.

The results of the present study appear to confirm the latter predictions. Examination of the dose-effect curves for both tasks at the conclusion of chronic ethanol injections indicated the expected decrease in ethanol sensitivity for FR performance, but a complete reversal of ethanol effects on DRL performance. Whereas initially ethanol produced only rate-decreasing effects on DRL performance, after extended intoxicated practice under the FR task, ethanol produced robust dose-related rate-increasing effects. In essence, the DRL task, known for its sensitivity to rate-increasing effects of drugs and other treatments, provided a sensitive marker for the presence of the rate-increasing strategy developed during intoxicated practice under FR conditions. Finally, consistent with our interpretation of the DRL-task rate increases as reflecting a compensatory process is the fact that only dose-related decreases in DRL responding were initially produced by ethanol. The concurrent FR/DRL task design appeared to have prevented the usual biphasic dose-effect pattern for ethanol's action on DRL performance seen in paradigms where the DRL task alone is performed.

At least one possible alternative interpretation of the DRL data from this present study is that the rate-increasing effects seen with this task may have been due to some nonspecific aftereffect of ethanol from the preceding afternoon's intoxicated practice session (i.e., a "hangover" effect). Indeed, we have just reported significant decreases in responding on an FR30 task during the initial phase of daily postsession ethanol injections (10). The postsession ethanol groups in that study did display some tolerance to ethanol's direct effects based solely on their behavioral adjustments to this delayed ethanol aftereffect. The present study did not include a postsession ethanol group and was not designed to address the presence of such delayed ethanol effects. However, when saline performance on the DRL and FR tasks were examined for the session immediately following the first dose-effect test for each task, overall responding on both tasks was slightly suppressed. With both ETOH and Controls combined, FR responding dropped to 80.4% of baseline ($p<0.05$) and DRL responding dropped to 87.5% of baseline ($p<0.10$). Although some delayed aftereffect of ethanol may be affecting operant performance, the direction of this effect on DRL performance was to decrease, not increase, responding. Further, the rate increases in DRL performance would not appear due to any learned compensation to any indirect effect of ethanol since the detailed IRT analysis indicated that the increased responding resulted in relatively fewer reinforcements at the end of the chronic ethanol period. Tolerance to ethanol's direct rate-increasing or rate-decreasing effects on DRL performance results in increases in reinforcements (1,2). Hence, the marked rate increases in DRL responding would appear to reflect a transfer of the learned adjustments to ethanol's direct effects on FR performance rather than some nonspecific aftereffect or to some secondary tolerance development on DRL performance per se.

On a more general level, what mediates the transfer of the learned compensatory behavior from the FR to the DRL task? One possibility is that the transfer is effected by some ethanol-induced state-dependency (19). That is, the ethanol state by its association with compensatory behaviors develop during intoxicated practice on the FR task may set the occasion for such behaviors during later tests with the DRL task. While this possibility cannot be excluded, modest rate-increasing effects were apparent in DRL performance during the period of daily presession saline injections. Other possible transfer-mediation factors would include the operant chamber context itself, more general aspects of lever-pressing for food, or even some interaction between these task characteristics and the direct effects of ethanol. LeBlanc and colleagues previously found generalization of tolerance developed to ethanol's effects on the shock-motivated moving belt task to performance on a food-motivated maze task (12). These authors suggested that some functional change in brain mechanisms induced by behaviorally augmented ethanol effects mediated their cross-tolerance results. While the precise basis for the latter cross-tolerance effect is conjecture at this point, the possibility that both functional neural adaptive changes as well as learned adaptive changes mediate tolerance to ethanol's behavioral effects depending on task characteristics. Indeed, Chen (3) has suggested that "in situations where the conditions of learning are favorable, processes or principles underlying learning or conditioning will be involved." From a learning perspective, one might expect tolerance based on learning to persist longer than tolerance based on functional brain tissue changes. Previous studies with the moving belt task have shown that tolerance developed to ethanol's effects on this task is lost within 2 weeks of cessation of ethanol administration [e.g., (13)]. In contrast, the tolerance developed in the FR operant task is known to persist partially for at least one month without intermittent ethanol tests and for at least six months with intermittent ethanol tests (2). Such long-term persistence for ethanol tolerance would appear more consistent with a learning interpretation at least for the operant task.

In summary, the present data support the hypothesis that tolerance to ethanol's effects on operant performance is largely based on the animal learning some compensatory behavioral adjustment. Further, the utilization of a concurrent task with differing reinforcement schedule characteristics appears to provide an effective way of detecting the presence of such acquired compensatory behaviors.

REFERENCES

1. Bird, D. C.; Holloway, F. A. Development and loss of tolerance to the effects of ethanol on DRL performance of rats. Psychopharmacology (Berlin) 97:45–50; 1989.
2. Bird, D. C.; Holloway, F. A.; Carney, J. M. Schedule-controlled behavior as an index of the development and loss of ethanol tolerance in the rat. Psychopharmacology (Berlin) 87:414–420; 1985.
3. Chen, C-S. Acquisition of behavior tolerance to ethanol as a function of reinforced practice in rats. Psychopharmacology (Berlin) 63: 285–288; 1979.
4. Demellweek, C.; Goudie, A. J. Behavioural tolerance to amphetamine and other psychostimulants. The case for considering behavioural mechanisms. Psychopharmacology (Berlin) 80:287–307; 1983.

5. Dickinson, A. Contemporary animal learning theory. Cambridge: Cambridge University Press; 1980:15–18.
6. Emmett-Oglesby, M. W.; Spencer, D. G.; Wood, C. M.; Lal, H. Task-specific tolerance to *d*-amphetamine. Neuropharmacology 23: 563–568; 1984.
7. Goudie, A. J. Behavioural techniques for assessing drug tolerance and sensitization. In: Boulton, A. A.; Baker, G. B.; Greenshaw, A. J., eds. Psychopharmacology. Neuromethods series. vol. 14. Clifton, NJ: Humana Press; in press.
8. Goudie, A. J.; Griffiths, J. W. An interdisciplinary approach to drug tolerance. Trends Pharmacol. Sci. 6:355–356; 1985.
9. Holloway, F. A.; Bird, D. C.; Holloway, J. A.; Michaelis, R. C. Behavioral factors in development of tolerance to ethanol's effects. Pharmacol. Biochem. Behav. 29:105–113; 1988.
10. Holloway, F. A.; King, D. A.; Michaelis, R. C.; Harland, R. D.; Bird, D. C. Tolerance to ethanol's disruptive effects on operant behavior in rats. Psychopharmacology (Berlin); in press.
11. LeBlanc, A. E.; Cappell, H. Tolerance as adaptation: interaction with behavior and parallels to other adaptive processes. In: Blum, K., ed. Alcohol and opiates: Neurochemical and behavioral mechanisms. New York: Academic: 1977:65–77.
12. LeBlanc, A. E.; Gibbons, R. J.; Kalant, H. Generalization of behaviorally augmented tolerance to ethanol, and its relation to physical dependence. Psychopharmacologia 44:241–246; 1975.
13. LeBlanc, A. E.; Kalant, H.; Gibbins, R. J.; Berman, N. D. Acquisition and loss of tolerance to ethanol by the rat. Psychopharmacologia 168:244–255; 1969.
14. Pohorecky, L. A. Effects of ethanol on central and peripheral noradrenergic neurons. J. Pharmacol. Exp. Ther. 189:380–391; 1974.
15. Pohorecky, L. A.; Brick, J. A new method for the determination of blood ethanol levels in rodents. Pharmacol. Biochem. Behav. 16: 693–696; 1982.
16. Prim, D. R.; Michaelis, R. C.; Holloway, F. A. Controlling operant behavior experiments with Commodore computers and PROMAL-software: Cost efficiency, "box bias," and speed. Soc. Neurosci. Abstr. 12:190; 1986.
17. Redmond, G. P.; Gohen, C. Sex differences in acetaldehyde exhalation following ethanol administration in C57/BL mice. Nature 236: 117–119; 1972.
18. Schuster, C. R.; Dockens, W. S.; Woods, J. H. Behavioral variables affecting the development of amphetamine tolerance. Psychopharmacologia 9:170–182; 1966.
19. Siegel, S. State-dependent learning and morphine tolerance. Behav. Neurosci. 102:228–232; 1988.
20. Torres, A.; Michaelis, R. C.; Holloway, K. J.; Holloway, F. A. A method for determining ethanol and acetaldehyde components from expired air samples in the rat. Soc. Neurosci. Abstr. 12:286; 1986.
21. Wenger, G. R. Cumulative dose-response curves in behavioral pharmacology. Pharmacol. Biochem. Behav. 13:647–651; 1981.
22. Wolgin, D. L. The role of instrumental learning in behavioral tolerance to drugs. In: Goudie, A. J.; Emmett-Oglesby, M. W., eds. Psychoactive drugs: Tolerance and sensitization. Clifton, NJ: Humana Press; 1989:17–114.