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Partial Cross-Dependence on Ethanol in Mice Dependent on Chlordiazepoxide[1]

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CHAN, A. W. K., M. C. LANGAN, F. W. LEONG, M. L. PENETRANTE AND D. L. SCHANLEY. *Partial cross-dependence on ethanol in mice dependent on chlordiazepoxide.* PHARMACOL BIOCHEM BEHAV **35**(2) 379–384, 1990.—Mice which had been fed chronically a liquid diet containing chlordiazepoxide (CDP) showed spontaneous and Ro15-1788-induced withdrawal signs upon CDP withdrawal. Ethanol (1.5 g/kg) injected 5 min before Ro15-1788 injection almost completely suppressed the withdrawal signs induced by the benzodiazepine receptor antagonist. However, neither ethanol injection nor ethanol diet administration could prevent the loss of appetite and weight loss on day 1 of CDP withdrawal. Likewise, the addition of saccharin in the ethanol diets did not prevent the loss of appetite. Mice which had been fed the CDP diet followed by 9 days of ethanol treatment (CDP/ethanol) showed more severe hypothermia during ethanol withdrawal compared to mice which had been fed the control/ethanol diets. The CDP/ethanol mice also retained the increase in runway activity attained from the prior CDP treatment. The data indicate that CDP-dependent mice showed partial rather than full cross-dependence on ethanol.

Ethanol-chlordiazepoxide cross-dependence Withdrawal signs Ethanol intake Ro15-1788 Benzodiazepine

ALTHOUGH cross-dependence between benzodiazepines (BZD) and ethanol has often been assumed (12, 16, 18), there has been only one study which demonstrates that ethanol-dependent mice are cross-dependent on chlordiazepoxide (CDP) (5). The experimental design followed the criterion suggested by Boisse and Okamoto (1), in which ethanol dependence was first produced in mice by administration of a liquid diet containing ethanol followed by substitution with a diet containing CDP. The substitution with CDP fully suppressed the manifestation of ethanol withdrawal signs. Upon withdrawal of the CDP diet, the mice showed CDP withdrawal signs (2,5). This paper describes experiments designed to investigate the reversed phenomenon, namely, that CDP-dependent mice are cross-dependent on ethanol. Specifically, the ability of ethanol to suppress CDP withdrawal signs and to maintain the dependence state acquired from prior CDP treatment was examined.

METHOD

Animals

Male C57BL/6J mice (8 weeks old) were purchased from Jackson Laboratories, Bar Harbor, ME. They were housed singly in plastic cages in a controlled-environment room (21–22°C) on an 11/13-hr light/dark cycle and received Teklad mouse diet (Teklad Mills, Winfield, IA) and tap water ad lib for 7–14 days before the beginning of an experiment.

Materials

CDP-hydrochloride and Ro15-1788 were gifts from Hoffmann-La Roche, Inc. (Nutley, NJ). Chocolate-flavored Sustacal liquid diet was purchased from Mead Johnson Nutritional Division (Evansville, IN). Ninety-five percent ethanol, USP, was from Aaper Chemical Co. (Shelbyville, KY) and vitamin diet fortification mixture was from Nutritional Biochemicals (Cleveland, OH).

CDP-Diet Administration

Detailed description of this method has appeared in another publication (8). The following summarizes the essential features. Mice were fed a liquid diet containing no CDP (control diet) for 3 days as the sole source of food and fluid. Thereafter, CDP (mg/ml) was incorporated in the diet as follows (concentrations and durations): 0.6, 3 days; 0.8, 3 days; 1, 3 days. From then on the CDP concentration was increased by 0.1 mg/ml daily, and the CDP diet was administered for another 18–25 days. Control mice were pair-fed the control diet.

CDP Withdrawal

Because of the changes in diet treatment after CDP withdrawal,

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each of the original two major groups (CDP-treated and control) was now further divided into two major groups, each having subgroups (N = 9 to 13 for each) of its own based on the kind of tests to be performed. The two phases (first/second) of diet treatment and major group designations are summarized as follows: Group A (CDP/ethanol): after CDP withdrawal these mice were given a choice of three ethanol diets ad lib (3.5, 5 and 6.5% v/v ethanol) (7) for 4 days followed by a choice of the 5 and 6.5% diets for the next 5 days. Group B (CDP/control): after CDP withdrawal these mice were pair-fed the control diet with group A. Group C (control/ethanol): these mice, which were originally pair-fed the control diet with group A, received the choice of ethanol diets ad lib as described for group A after the first withdrawal. Group D (control/control): after the first withdrawal, these mice continued to be pair-fed the control diet with group A.

At least one subgroup from each of the above diet treatment groups was monitored for Ro15-1788-induced withdrawal following removal of the CDP diet. The dose of Ro15-1788 was 25 mg/kg. The ability of ethanol (acute injection of 1.5 or 2.5 g/kg) to suppress Ro15-1788-induced withdrawal was also investigated. Therefore, mice involved in this particular experiment were injected with either saline or ethanol 5 or 15 min before the injection of Ro15-1788. The following withdrawal signs were scored, based on the combination and modification of the methods of Gallaher *et al.* (10) and Goldstein (11). (a) *Handling-Induced Seizures:* 0 = no seizure when mouse is turned 180°, 1 = seizure occurs when mouse is turned 180°, 2 = seizure occurs when mouse is gently "tickled," 3 = seizure occurs when mouse is picked up by the tail, 4 = spontaneous seizure in home cage. (b) *Tremor:* 0 = none, 1 = fine body tremor, 2 = coarse tremor with mildly impaired locomotion, 3 = marked coarse tremor, marked impairment of locomotion, 4 = severe coarse tremor, falls during locomotion. (c) *Tail Lift:* 0 = flattened to floor, 1 = horizontal, 2 = 45° lift, 3 = 90° lift, 4 = retrograde, over back. (d) *Locomotion:* 0 = normal exploratory movement with rearing, 1 = slow movement, with few rearing, 2 = deliberate/slow movement, no rearing, 3 = very slow movement, virtually stationary, 4 = turning slowly in circles, or moving slowly backward.

Spontaneous withdrawal signs such as body weight changes and loss of appetite were also monitored after CDP diet withdrawal. The effects of ethanol diet consumption with or without supplementary ethanol injections on these parameters were examined.

Ethanol Withdrawal

On the day that the ethanol diets were withdrawn, mice whose diet treatment history was CDP/ethanol or control/ethanol were fed ad lib the control diet, while those which had been fed CDP/control or control/control were still pair-fed the control diet. Ethanol withdrawal signs such as hypothermia, handling-induced seizures and tremor were monitored as described previously (7).

Runway Test

On selected days after withdrawal of the first diet (i.e., CDP), the CDP-dependent mice and their pair-fed controls were tested for runway activity. The apparatus and testing procedure have been described in another publication (5). In order to test whether the ingestion of ethanol diet would alter the long-term effects of the previous CDP treatment on runway activity, mice whose diet treatment history was CDP/ethanol or control/ethanol were also tested on selected days after ethanol withdrawal.

RESULTS

Effect of Ethanol on Ro15-1788-Induced CDP Withdrawal

Injection of ethanol (1.5 or 2.5 g/kg, but only data for the lower dose are shown) almost completely suppressed the withdrawal signs induced by Ro15-1788 injection 5 min later (Fig. 1). The data for pair-fed control mice were not shown because Ro15-1788 did not induce any quantifiable withdrawal signs in these animals.

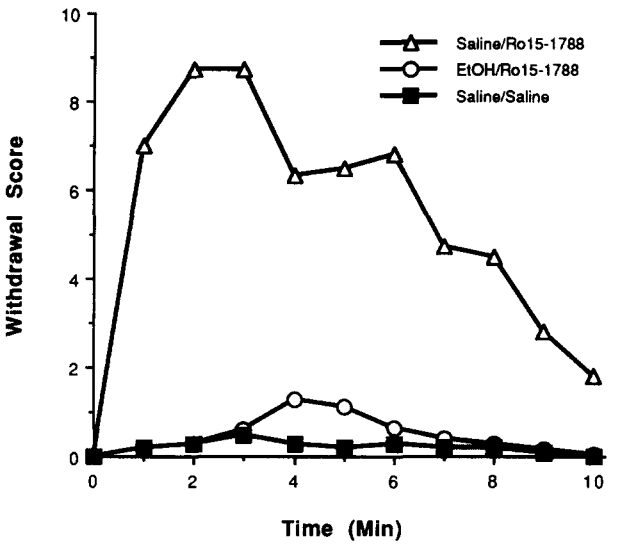

FIG. 1. Effect of ethanol on Ro15-1788-induced CDP withdrawal. Values are means of cumulative withdrawal scores for 7 to 11 mice in each group. Mice were injected with saline or ethanol (1.5 g/kg) five min before the injection of Ro15-1788 (25 mg/kg). Times shown are those after Ro15-1788 injection.

Effect of Ethanol on Spontaneous CDP Withdrawal

Figure 2 compares ethanol intake between CDP-dependent and pair-fed control mice after CDP withdrawal. On day 1 of withdrawal, the CDP-dependent mice consumed significantly less of the ethanol diets than the pair-fed control mice, irrespective of whether the intake was expressed in total volume, $F(1,18) = 55.8$, $p<0.001$, or in g/kg, $F(1,18) = 182$, $p<0.001$. Therefore, unlike the ability of injected ethanol to suppress Ro15-1788-induced withdrawal signs, the availability of ethanol diets did not prevent the loss of appetite, a symptom frequently observed on day 1 of spontaneous CDP withdrawal (5). On day 2, the total volume was not significantly different between the two groups, $F(1,18) = 3.9$, $p>0.05$; however, the pair-fed control mice still had a higher ethanol intake when it was expressed in g/kg, $F(1,18) = 6.1$, $p<0.05$. For the rest of the ethanol diet administration period, the total intake of ethanol (volume or g/kg) was not significantly different between the two groups, except for day 6 when the CDP-dependent mice had a lower ethanol intake, 15.3 vs. 20.7 g/kg, $F(1,18) = 10.0$, $p<0.01$.

The effects of ethanol injection and administration of ethanol diets on weight loss during day 1 of CDP withdrawal (spontaneous or Ro15-1788-induced) are shown in Fig. 3. The CDP-dependent mice which were injected with saline/saline and subsequently fed the control diet had significantly more weight loss on day 1 than CDP-dependent mice which were injected with saline/ethanol, ethanol/Ro15-1788 or saline/Ro15-1788 (Fig. 3A); $F(3,36) = 8.9$, $p<0.001$. The latter three groups did not differ in the magnitude of weight loss. Therefore, ethanol injection did not alleviate this symptom in mice undergoing spontaneous or Ro15-1788-induced withdrawal. These three groups of mice also had comparable body weight losses on days 1 to 3 when they were fed

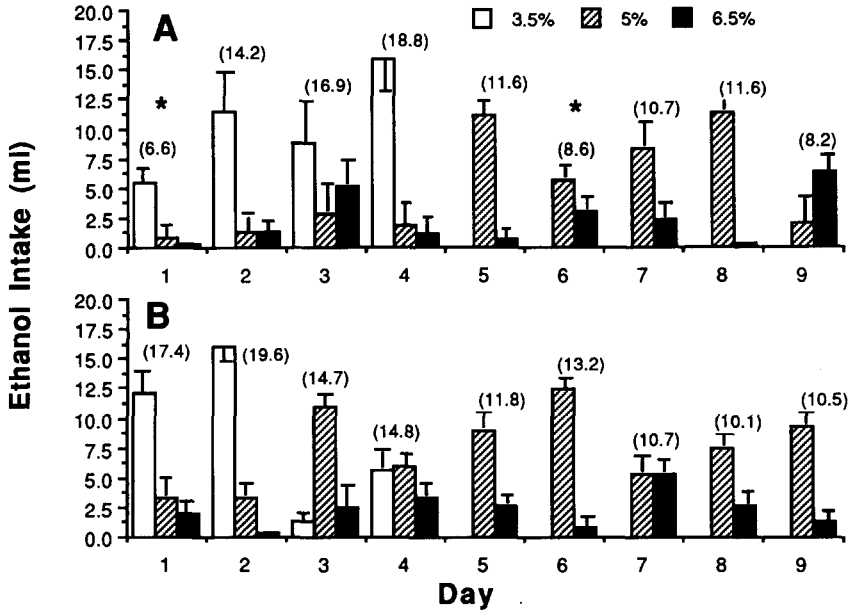

FIG. 2. Ethanol intake after CDP withdrawal. Panels A and B show data for mice previously fed the CDP diet or control diet, respectively. Numbers in parentheses represent total daily intake. *$p<0.01$.

ad lib the choice of ethanol diets (Fig. 3B). The recovery of weight loss was much slower in mice fed the ethanol diets than those fed the control diets (Fig. 3A vs. Fig. 3B). Although not shown in Fig. 3, pair-fed control mice with similar injection treatments all gained weight (2 to 3 g) on day 1, irrespective of whether they were fed ad lib the control diet or ethanol diets.

Since the much lower intake of ethanol diets by the CDP-dependent mice on day 1 of CDP withdrawal might have been partially caused by a taste aversion developed from the chronic CDP diet treatment, we have tested whether the inclusion of saccharin (0.05 or 0.1%) in the ethanol diets could enhance ethanol intake by the mice. The data shown in Table 1 indicate that incorporation of saccharin had no significant effect on ethanol intake in the CDP-dependent mice (conditions a, b, c). Because of space limitations only data for selected days are shown in Table 1, but the results for the other days were comparable. Data for the pair-fed control mice also indicate that in general saccharin had little or no effect on ethanol consumption, except on days 2 and 4, during which the mice consumed significantly less of the ethanol diet containing 0.05% saccharin [e.g., day 4, $F(2,30)=5.6$, $p<0.01$]. The results shown in Table 1 confirm those described earlier in Fig. 2, namely, that CDP-dependent mice had significantly less ethanol intake (g/kg) than the pair-fed control mice on days 1 and 2 of CDP withdrawal. However, the results for day 6 in Fig. 2 were not reproduced in the experimental data shown in Table 1.

Ethanol Withdrawal

On the day of ethanol diet withdrawal, mice which had been fed the CDP/ethanol diets had significantly more severe withdrawal hypothermia at 3 and 7 hr than mice whose diet histories were control/ethanol [Fig. 4; e.g., at 3 hr, $F(1,37)=5.1$, $p<0.05$]. The data are consistent with the hypothesis that substitution of CDP with ethanol can maintain at least part of the dependence state acquired from the previous CDP treatment. Mice which had been fed either CDP/control or control/control did not show withdrawal hypothermia. Other potential withdrawal signs such as tremor, tail lift and handling-induced seizures did not appear with sufficiently reliable frequencies and severity to be quantified. This is because of the experimental design which led the mice to choose more of the ethanol diet containing the lowest concentration of ethanol. Therefore, mild withdrawal symptoms were to be expected, e.g., there was no weight loss or loss of appetite on day 1 of ethanol withdrawal in either the CDP/ethanol or control/ethanol mice.

Runway Test

On selected days after CDP withdrawal, the CDP-dependent mice showed significant increases in runway activity compared to pair-fed control mice (Fig. 5A). Both groups of mice were fed the control diet after CDP withdrawal. These data confirm those reported earlier in a preliminary communication (3). Although only data up to day 30 of CDP withdrawal are shown in Fig. 5A, the rebound increase in runway activity lasted more than 90 days in another experiment. As depicted in Fig. 5B, mice which had been fed the CDP diet followed by the ethanol diet (CDP/ethanol) also showed increases in runway activity after ethanol withdrawal compared to mice which had been fed control/ethanol diets. Thus, the ethanol diet treatment did not affect the increase in runway activity acquired from the prior CDP diet treatment.

DISCUSSION

Because of the similar pharmacological actions of ethanol and BZD, and because BZD are well known for their ability to suppress ethanol withdrawal symptoms, cross-dependence between ethanol and BZD has often been assumed. However, drugs that can suppress alcohol withdrawal signs may not necessarily be cross-dependent on ethanol because BZD may suppress ethanol withdrawal signs due to their anticonvulsant, sedative and antianx-

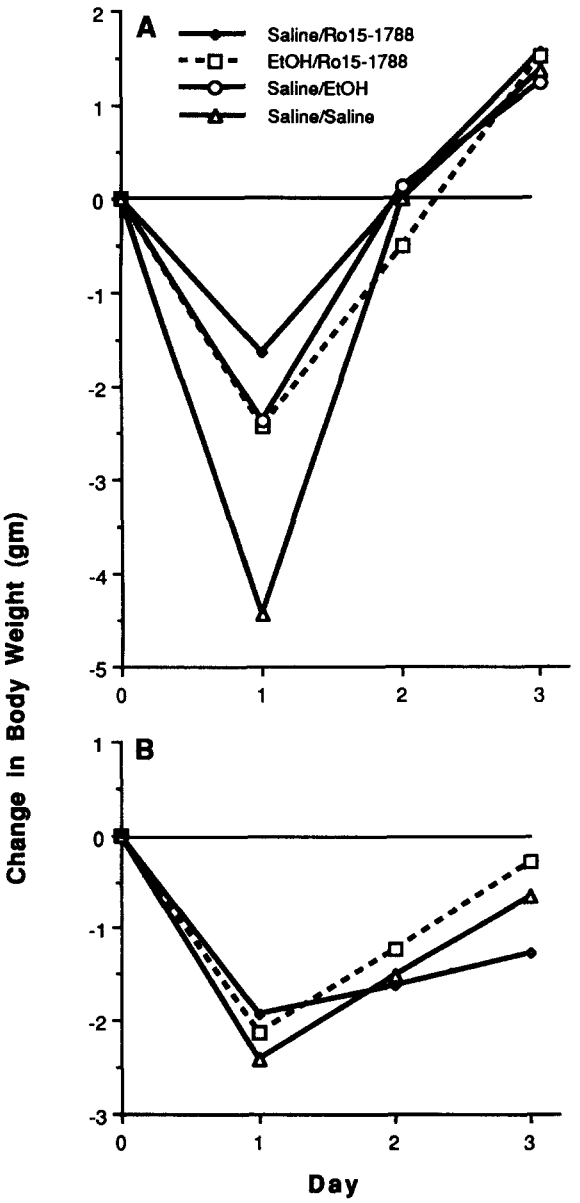

FIG. 3. Body weight changes after CDP withdrawal. Day zero was the day when the CDP diet was withdrawn. Values are mean differences (N = 7 to 11 in each group) between the daily weights and the respective 0 day values. Panel A: Mice were fed the control diet ad lib after CDP withdrawal. Panel B: Mice were fed the choice of ethanol diets after CDP withdrawal.

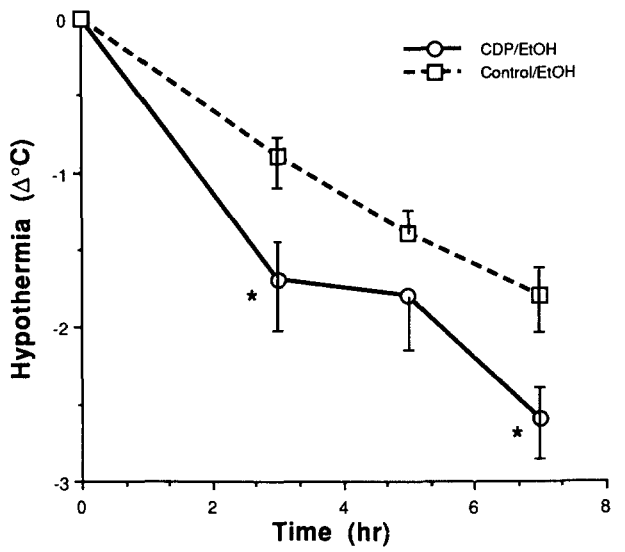

FIG. 4. Rectal temperature changes after ethanol withdrawal. Times shown are those after removal of the ethanol diets (at time zero). Values are mean differences (± S.E.) between rectal temperature at selected time intervals and the respective temperature at time zero. *$p<0.05$.

iety properties rather than because they are fully substitutable with ethanol. Although anecdotal accounts of alcoholics using alcohol and BZD interchangeably are available (17), practical, humane, and ethical considerations preclude any well-controlled studies to demonstrate cross-dependence between alcohol and BZD in man. Therefore, animal models have to be substituted. In a previous study (5), we have demonstrated cross-dependence on CDP in ethanol-dependent mice by following the criterion suggested by Boisse and Okamoto (1) for testing cross physical dependence: ". . . the bidirectional experiment of producing dependence on one drug, then substituting the other must be done. The criterion of equivalence is satisfied when the substitution drug fully suppresses the manifestation of withdrawal from the first and maintains the dependence until it is allowed to manifest in a quantifiable withdrawal reaction." However, these data do not indicate that the reverse phenomenon, namely, that CDP-dependent mice are cross-dependent on ethanol, should necessarily be true. In investigations of drug tolerance and cross-tolerance, it has been shown that chronic treatment of rats with CDP conferred full cross-tolerance to ethanol, but prior treatment with ethanol only conferred partial cross-tolerance to CDP (15). In contrast, Chan *et al.* (6) reported that ethanol tolerance conferred full cross-tolerance to CDP if the tests for tolerance were hypothermia or the horizontal dowel test, but only partial cross-tolerance to CDP was observed in the runway test, while no cross-tolerance to CDP was detected in the head-dipping test. Although the relationship between cross-tolerance and cross-dependence has not been established, these data suggest that both directions of cross-dependence between ethanol and CDP (cross-dependence on ethanol in CDP dependency and cross-dependence on CDP in ethanol dependency) need to be investigated.

The data presented in this study demonstrate that although ethanol could almost fully suppress Ro15-1788-induced withdrawal signs (Fig. 1), neither ethanol injection nor ethanol diet administration suppressed the loss of appetite and weight loss commonly seen on day 1 of spontaneous CDP withdrawal (Fig. 2 and Fig. 3). It is possible that the lower intake of ethanol diet in the CDP-dependent mice might be triggered by the mice experiencing the combined sedative effect of ethanol and CDP or its N-desmethyl metabolite (NDCDP) which is known to be more than additive (4). However, this is deemed unlikely because our previous studies (2,5) have shown that, despite the same potential for ethanol-CDP interaction, ethanol-dependent mice consumed large amounts of CDP diets soon after ethanol withdrawal (5). Moreover, we have also conducted experiments (results not shown in this paper) in which the ethanol diets were not given to the CDP-dependent mice until several hours after CDP withdrawal, the rationale being to allow residual levels of CDP or NDCDP to be lowered to minimize ethanol-CDP (or NDCDP) interactions.

TABLE 1

INTAKE OF ETHANOL DIETS AFTER CDP WITHDRAWAL: EFFECTS OF SACCHARIN

Prior Diet Treatment		Total Ethanol Intake (g/kg)* Day 1	Day 2	Day 4	Day 6	Day 8
CDP	a)	5.11 ± 0.79	15.23 ± 1.26	20.08 ± 0.91	17.38 ± 1.33	15.28 ± 1.62
	b)	7.62 ± 0.79	12.99 ± 1.14	18.96 ± 1.56	18.02 ± 0.85	16.34 ± 1.16
	c)	6.86 ± 1.02	15.73 ± 1.40	19.49 ± 1.25	16.91 ± 1.23	16.12 ± 1.12
Pair-Fed Control	a)	23.13 ± 0.68	23.56 ± 0.76	19.75 ± 1.25	19.61 ± 1.20	22.55 ± 2.14
	b)	21.47 ± 1.08	19.54 ± 1.67†	14.82 ± 1.03†	16.36 ± 0.82	18.12 ± 1.13
	c)	23.20 ± 0.76	23.80 ± 1.23	18.08 ± 0.86	15.59 ± 1.96	21.63 ± 1.81

a = ethanol diets without saccharin.
b = ethanol diets containing 0.05% saccharin.
c = ethanol diets containing 0.1% saccharin.
*Calculations based on volume of intake and ethanol concentration of each diet, and body weight. Values are means ± S.E. (N = 10 or 11 each group).
†Significantly different ($p<0.05$) from conditions a and c of pair-fed control mice.

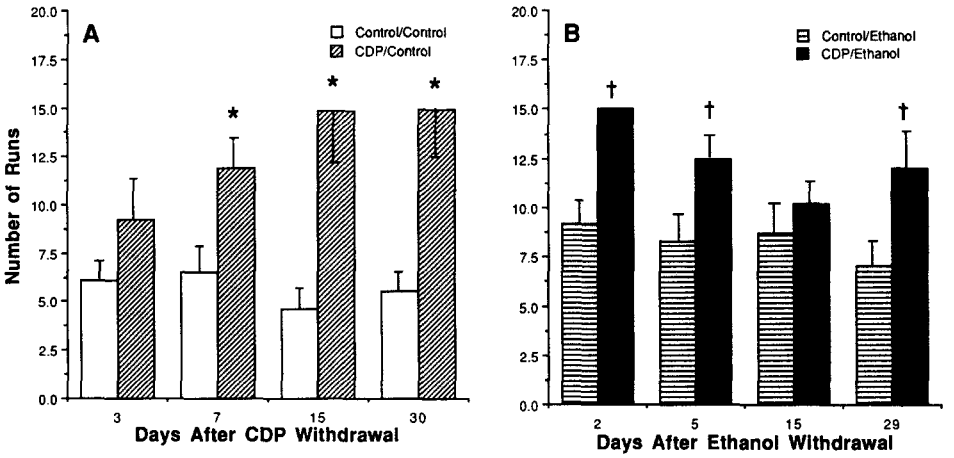

FIG. 5. Runway activity after CDP (panel A) or ethanol (panel B) withdrawal. Panel A: Data for mice which had been fed the CDP diet followed by the control diet, and mice which had been fed the control diet in both phases of the experiment. Panel B: Data for mice which had been fed the CDP diet followed by ethanol diet treatment, and mice which had been fed the control diet followed by ethanol diet treatment. Values are means ± S.E. (N = 9 to 11 in each group). *$p<0.005$; †$p<0.02$.

This approach also did not result in an increase in the intake of ethanol diets. The recovery of weight loss was slower in the CDP-dependent mice treated with the choice of ethanol diets, compared to that seen in CDP-dependent mice given the control diet. Taken together these data indicate that ethanol cannot fully substitute for CDP in CDP-dependent mice. Despite this partial equivalence between CDP and ethanol, mice which had been treated with CDP/ethanol diets had more severe ethanol withdrawal hypothermia than mice which had been treated with control/ethanol diets (Fig. 4). The more severe withdrawal hypothermia was not due to a higher intake of ethanol by the CDP/ethanol mice. In fact, these mice consumed less of the ethanol diets on day 1 and day 2 of CDP withdrawal than the pair-fed control mice (Fig. 2 and Table 1). The results can be interpreted as the ability of ethanol to maintain at least part of the dependent state acquired from the prior treatment of CDP. An alternative interpretation is that prior dependence on CDP facilitated the development of ethanol dependence. Unfortunately, because of the mild ethanol withdrawal, withdrawal signs other than hypothermia could not be quantified. Investigations are in progress to examine whether ethanol can maintain the tolerance state acquired from the prior treatment of CDP.

There has also been limited information concerning cross-dependence between ethanol and other pharmacologically similar drugs, e.g., the barbiturates. Data from one human study (9) and from one animal study (19) indicate that alcohol is a partial substitute for barbiturates in patients and animals chronically exposed to barbiturates. Other indirect pharmacological studies suggest that different mechanisms are involved in the development of ethanol and barbital physical dependence (13,14). The inability of ethanol to fully suppress spontaneous CDP withdrawal signs may reflect that different mechanisms are involved in the development of ethanol and CDP dependence. The pharmacological properties of BZD are ideally suited for the suppression of ethanol

withdrawal symptoms, especially in light of the fact that the neurochemical actions of BZD can counteract many of the neurochemical changes associated with ethanol withdrawal [Chan, A. W. K. The role of benzodiazepines in alcohol withdrawal seizures. In: Porter, R.; Mattson, R.; Cramer, J.; Diamond, I., eds. Alcohol and seizures. Philadelphia, PA: F. A. Davis; 1989:in press]. Some of these neurochemical changes might cause the manifestation of ethanol withdrawal signs. The neurochemical mechanisms involved in the development of BZD dependence have not been investigated to any great extent. Therefore, we can only speculate that the inability of ethanol to fully suppress spontaneous CDP withdrawal might be due to the incompatibility between the actions of ethanol and the neurochemical bases of CDP withdrawal.

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