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Effects of Parachlorophenylalanine on Ethanol Self-Selection in the Rat[1]

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PARKER, L. F. AND B. L. RADOW. *Effects of parachlorophenylalanine on ethanol self-selection in the rat.* PHARMAC. BIOCHEM. BEHAV. 4(5) 535–540, 1976. – The efficacy of p-chlorophenylalanine (PCPA) in producing conditioned taste aversions and unconditioned avoidance of ethanol was investigated in two experiments. It was found that administering PCPA to rats having free access to a saccharine solution and water produced robust aversions to saccharin that extinguished within 6 days after termination of the PCPA treatments, thereby indicating that PCPA can produce conditioned aversions to substances consumed during its administration. In a second experiment, intraperitoneal injections of PCPA and/or ethanol given to rats not having access to ethanol were found to produce no change in their subsequent ethanol preferences. The results support the contention of earlier investigators that the reported effects of PCPA on the rat's preference for ethanol may have been due largely to the animals acquiring conditioned aversions to ethanol during PCPA treatments.

Ethanol self-selection p-Chlorophenylalanine Serotonin depletion Conditioned taste aversions

RECENTLY several drugs have been found to be capable of reducing self-selection of ethanol by laboratory animals [2, 4, 10]. In particular, Myers and Veale [10] reported in 1968 that parachlorophenylalanine (PCPA), a tryptophan hydroxylase inhibitor that depletes the brain of serotonin [1,5], caused rats to show strong aversions to ethanol when PCPA induced serotonin depletion occurred concurrently with ethanol consumption. In this and subsequent studies, Myers and co-workers have demonstrated that PCPA can induce ethanol aversions that become even stronger when PCPA treatments are terminated [6, 8, 9, 10, 17]. They have interpreted these findings as suggesting that PCPA may cause some kind of non-reversible metabolic change that makes the postingestional effects of ethanol aversive to the rat (i.e., [10]).

Since the rat can readily associate the consumption of an unfamiliar substance with a postingestional occurance of toxicosis, and will manifest conditioned aversions to the tastes of such substances [3, 13, 15, 16], Nachman *et al.* [11] alternatively suggested that rats treated with PCPA while having access to ethanol may have associated the noxious effects of PCPA with ethanol consumption and, hence, manifested conditioned aversions to ethanol. That PCPA induced ethanol aversions were due to conditioning, rather than to an interaction between PCPA's pharmacological effects and ethanol metabolism, was indicated by their finding that PCPA caused rats to avoid consuming a saccharin solution, as well as ethanol, if consumption of these fluids was immediately followed by an injection of PCPA [11]. Since saccharin is metabolically inert, it was reasoned that PCPA induced aversions could be obtained without regard to possible interactions between the manner in which the avoided substance was metabolized and the pharmacological effects of PCPA. They therefore concluded that the occurrence of ethanol aversions in PCPA treated rats, as reported by Myers and Veale [10], was probably due to conditioning [11].

There are, however, several important shortcomings in the experiments by Nachman *et al.* [11] that make such a conclusion untenable. First, the finding that PCPA can produce conditioned taste aversions (i.e., saccharin aversions) does not, of course, demonstrate that PCPA induced ethanol aversions are similarly due to conditioning. Stronger evidence is required such as a failure to find PCPA induced ethanol aversions under conditions that would preclude such conditioning. At best, then, the data of Nachman *et al.* [11] suggest that some of PCPA's effect on ethanol preferences may have been due to the animals acquiring conditioned taste aversions to ethanol.

Even this suggestion is only weakly supported by the findings of Nachman *et al.* [11], however, because the conditions of their experiments served to optimize the probability that conditioned taste aversions would result from PCPA treatments. That is, Nachman *et al.* [11]

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employed two conditions in their experimental design that have been found to enhance the strength of conditioned taste aversions [14, 15, 16]: (1) their animals were not allowed to become familiar with the solutions prior to conditioning procedures, and (2) they contingently administered PCPA to their animals immediately after they had consumed the taste solutions.

Myers and his co-workers, on the other hand, administered PCPA noncontingently to rats that had been allowed continuous access to ethanol for 11 [10] to 77 [17] days prior to PCPA treatments. These conditions are not nearly so favorable for the production of conditioned taste aversions as those employed by Nachman *et al.* [11], and it is therefore not clear that the PCPA induced ethanol avoidance reported by Myers and co-workers (i.e., [10]) was due to conditioning at all.

To determine the extent to which conditioning factors may have been responsible for PCPA's reported effect on ethanol preference in the rat, the following experiments were designed after the "noncontingent" procedures of Myers and his co-workers (e.g., [10]) such that in Experiment 1 the efficacy of their procedure in producing conditioned taste aversions could be assessed independently of PCPA's possible effects on ethanol preference, and in Experiment 2 the effects of PCPA on ethanol preference could be assessed independently of conditioning factors that might possibly affect ethanol preferences.

EXPERIMENT 1

As suggested by Nachman *et al.* [11], a reduction in preference for a metabolically inert saccharin solution caused by treatments with PCPA would be substantial evidence for the drug's capacity to produce conditioned taste aversions independently of its possible effects on the metabolism of such an avoided substance. Whether PCPA could produce conditioned taste aversions under conditions similar to those in which Myers and Veale [10] and others [2, 6, 8, 9, 17] reported finding a PCPA induced avoidance of ethanol was thus determined in the following experiment by substituting a solution sweetened with sodium saccharin for ethanol in the experimental design of Myers and Veale [10].

METHOD

Animals

Fourteen experimentally naive male rats of the Wistar strain were used. The animals were obtained from the colony maintained by the Psychology Department of the University of Washington where they were housed in large colony cages (12 rats/cage) until initiation of the experiment, at which time all animals were housed in individual stainless steel cages. The rats were approximately 120 days old and weighed between 275 and 310 g.

Procedure

The procedure was similar to that of Myers and Veale [10] with the exception that a 0.23% (w/v) sodium saccharin solution was substituted for ethanol in their paradigm. All animals received three 11-day saccharin preference tests; one prior to drug treatments, another during drug treatments, and a postdrug preference test. Preference scores for the saccharine solution were obtained using the three-bottle, two-choice, random-rotation method of Myers and Holman [7]. Preference for saccharin of each animal was calculated by dividing the amount of saccharin consumed by the sum of saccharin and water consumption. Saccharin, water, and Purina Laboratory Chow were continuously available during the tests, and consumption of water and saccharin were recorded daily for each animal. The 11-day preference tests were separated by one day on which all animals were offered only water and food.

During the second preference test half of the animals received daily intraperitoneal injections of PCPA in a dose of 300 mg/kg (the PCPA was generously supplied by Dr. Albert Weissman of Chas. Pfizer and Co.), and the remaining half received daily intraperitoneal injections of the vehicle in equivalent volumes. The PCPA was suspended in 5% gum acacia in a concentration of 50 mg/cc. We have found this PCPA dose and route of administration to deplete brain serotonin levels to less than 10% of control levels within 3 days of a single injection [1].

RESULTS AND DISCUSSION

The saccharin preference scores of the two groups during the 3 preference tests are shown in Fig. 1. As depicted, all animals showed strong preferences for the saccharin solution during the baseline preference test. During the drug treatment preference test, however, the rats injected with PCPA developed marked aversions to the saccharin solution and avoided consuming it throughout the remainder of the test. Upon discontinuation of PCPA treatments their aversions began to dissipate and approached the control group's preference for saccharin with 6 days. During the drug treatment preference test the PCPA animals showed a mean body weight loss of 15%, whereas the control animals showed a mean weight gain of 3%.

The robust saccharin aversions manifested by the PCPA treated rats during the drug treatment preference test indicate that rats can associate the consumption of a relatively unfamiliar substance (i.e., saccharin was less familiar than water or laboratory chow) with the noxious effects of PCPA [11], and that indeed such aversions can develop under experimental conditions similar to those of Myers and Veale [10] and others [2, 6, 8, 9, 17]. Such robust aversions are rather surprising in light of the prior experience the rats were given with saccharin and the noncontingent association of PCPA treatments with saccharin consumption ([14, 15, 16]; but see [12,13]).

That the PCPA treated animals' aversions to saccharin rapidly extinguished when PCPA treatments were discontinued suggests that the capacity of PCPA to produce conditioned taste aversions may be independent of its ability to deplete brain serotonin. That is, similar doses of PCPA have been found to deplete brain serotonin to less than ten per cent of control levels, with the time of peak effect occurring between the second and third postinjection day, and normal serotonin levels were not recovered until approximately the sixteenth postinjection day [1,4]. Hence, PCPA induced depletion of serotonin was probably still severe during the time in which the PCPA induced saccharin aversions dissipated in Experiment 1, and some more transient effect of PCPA must have caused the animals to avoid consuming the saccharin solution.

EXPERIMENT 2

The findings of Experiment 1 indicate that PCPA can

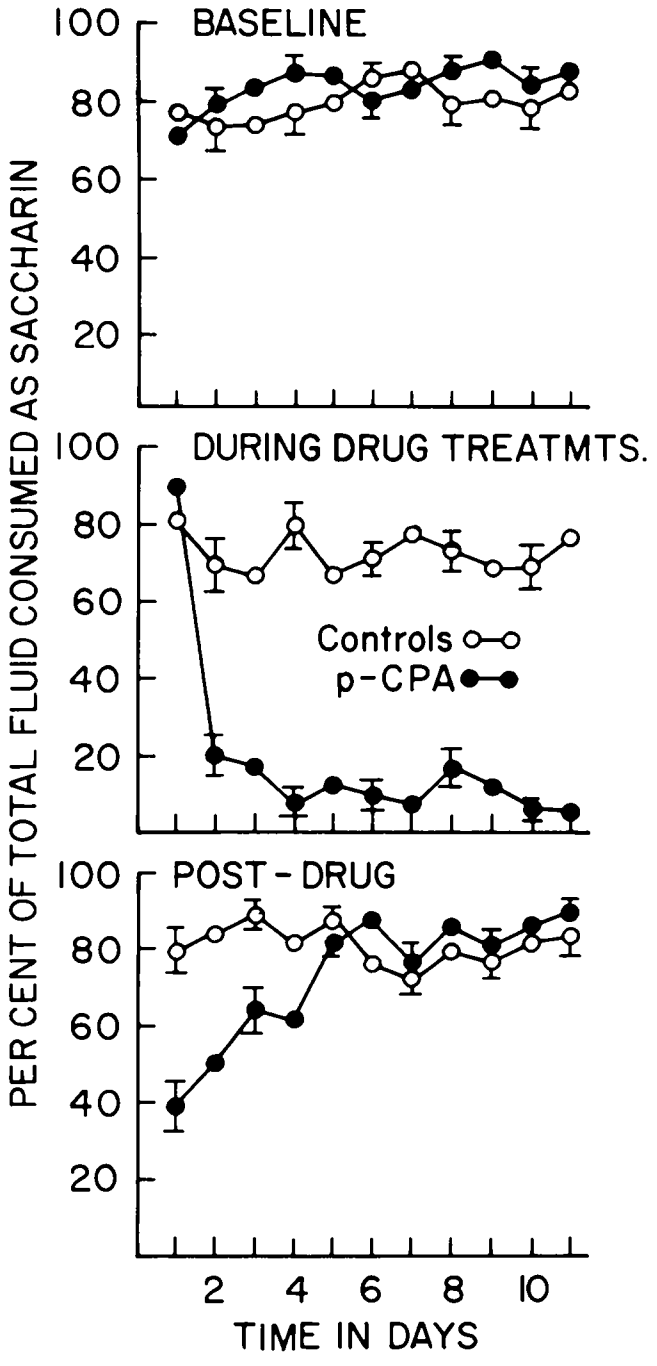

FIG. 1. Mean saccharin preferences for the two groups during the three saccharin vs water preference tests. Vertical bars indicate standard errors of the means.

produce conditioned taste aversions to a relatively unfamiliar taste solution in the experimental design of Myers and Veale [10]. The remaining question, then, concerns whether such conditioning can solely account for PCPA's ability to produce ethanol aversions [2, 6, 8, 9, 10, 17]. The finding that PCPA induced saccharin aversions observed in Experiment 1 rapidly extinguished upon termination of PCPA injections (see Fig. 1) makes it questionable that such conditioning was responsible for the prolonged ethanol aversions reported by Myers and Veale [10].

The purpose of this experiment, therefore, was to determine whether PCPA can cause rats to avoid consuming ethanol under conditions that should preclude the formation of a learned association between ethanol consumption and the noxious effects of PCPA treatments.

METHOD

Animals

Twenty-eight experimentally naive male rats of the Wistar strain, obtained from the colony maintained by the Psychology Department at the University of Washington, were housed in individual stainless steel cages with ad lib Purina Laboratory Chow and water. The animals were approximately 120 days old and weighed between 305 and 387 g.

Procedure

Again, the procedure was similar to that of Myers and Veale [10], with the exception that the animals were not given access to ethanol either during the PCPA treatment nor during a 16-day postinjection recovery period. Two 11-day ethanol preference tests were administered to all animals; one was initiated 12 days prior to an 11-day drug treatment period and the other was initiated 16 days after the drug treatments. The intervening 11-day drug treatment regimen combined daily injections of ethanol, PCPA, and their vehicles in a 2 x 2 factorial design (N = 7/group). That is, Group (PCPA) received daily intraperitoneal injections of PCPA (300 mg/kg) at 1400 hr. Group (PCPA + ETOH) received intraperitoneal injections of ethanol (2 g/kg) twice daily at 800 hr and 2000 hr, and a daily injection of PCPA (300 mg/kg) at 1400 hr. Group (ETOH) received similar injections of ethanol twice daily at 800 hr and 2000 hr. Group (Veh) received daily intraperitoneal injections of the PCPA vehicle (5% gum acacia) at 1400 hr. Water and laboratory chow were available ad lib during the 11-day drug treatment period and the subsequent 16-day recovery period.

Ethanol solutions for injection were diluted from 95% ethanol to a concentration of 20% (w/v) by adding distilled water. The PCPA was suspended in 5% gum acacia in a concentration of 50 mg/cc.

Ethanol preference scores were obtained, as described by Myers and Veale [10], by offering all animals free access to both water and ethanol solutions in a daily ascending concentration sequence of 3, 4, 5, 6, 7, 9, 12, 15, 20, 25, and 30 percent (v/v). The ethanol solutions and water were presented to the animals using the three-bottle, two-choice, random-rotation method [7,10]. Purina Laboratory Chow was available ad lib throughout both preference tests.

In summary, then, the procedure consisted of obtaining baseling ethanol preference scores, treating the animals with injections of PCPA and/or ethanol or sham injections while the animals did not have access to ethanol, and, following a 16-day recovery period, obtaining postdrug treatment ethanol preferences. Since the animals were not given an opportunity to consume ethanol during the drug treatments and subsequent recovery period, the possibility of the animals forming conditioned aversions to ethanol was precluded. Thus, a significant change in ethanol preference after PCPA treatments (Group (PCPA)) could be attributed

directly to the effects of PCPA. If PCPA's reported effects on ethanol preference in rats [2, 6, 8, 9, 10, 17] were due to some interaction between PCPA and ethanol that may have occurred in animals having access to ethanol during PCPA treatments, such effects should be revealed by comparisons of the baseline and postdrug treatment ethanol preferences of Group (PCPA + ETOH). Group (Veh) and Group (ETOH) served to control for possible effects that the injection procedures and ethanol administration may have had on ethanol preferences.

RESULTS AND DISCUSSION

The mean ethanol preferences of the four groups obtained before and after the drug treatments are shown in Fig. 2. The four groups showed typical preferences for the various ethanol solutions during both the baseline and postdrug treatment preference tests [7,10], manifesting relatively high preferences for ethanol in low concentrations and avoiding ethanol in high concentrations. As depicted in Fig. 2, it appears that groups (PCPA + ETOH) and (ETOH) showed somewhat lower overall ethanol preferences than groups (Veh) and (PCPA) both during the baseline and post-drug treatment preference tests. Since the former two groups were run after the data had been collected from the latter, statistical evaluations of the apparent differences in ethanol preferences between the groups would be meaningless and only within group statistical tests were performed.

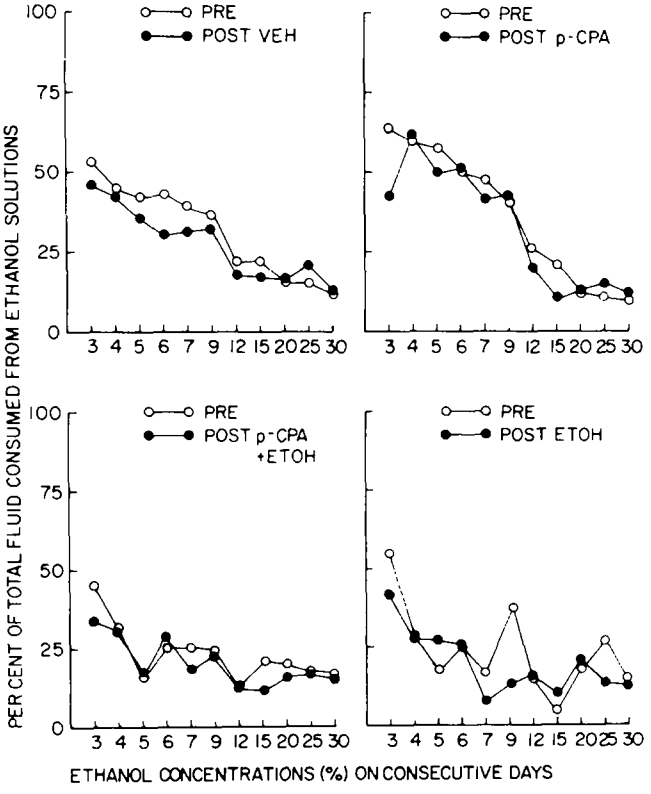

FIG. 2. Mean ethanol preferences of the four groups given access to water and various concentrations of ethanol both before (open circles) and after (closed circles) drug treatments.

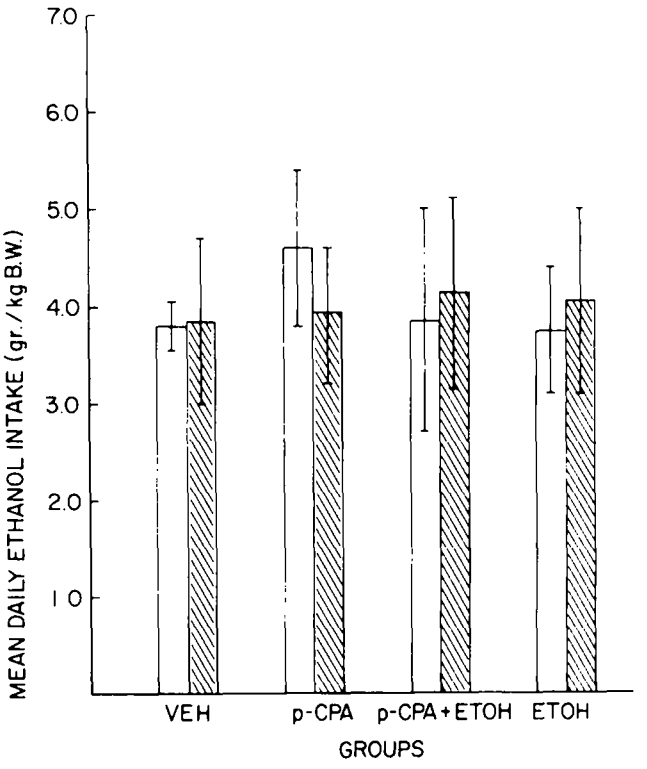

FIG. 3. Mean daily intake of absolute ethanol in g per kg body weight of the four groups before (open columns) and after (shaded columns) drug treatments. Values were calculated from the consumption scores for 3–30% ethanol during the preference tests. Vertical bars indicate standard errors of the means.

Inspection of Fig. 2 suggests that the four groups all showed a slight reduction in ethanol preference during the postdrug treatment preference test. Analyses of variance applied to the baseline and postdrug treatment ethanol preference scores of the various groups revealed that there were no significant differences in overall ethanol preferences after drug treatments within any of the groups (Group Veh, $F = 2.14$; Group PCPA, $F = 1.36$; Group PCPA + ETOH, $F = 1.87$; Group ETOH, $F = 1.93$; $1/152$ df and $p>0.05$ in all tests). Thus, administering PCPA or both PCPA and ethanol, without allowing the animals concurrent access to ethanol, did not significantly affect their overall preferences for ethanol.

The ethanol consumption of the animals in the four groups during both preference tests was calculated as g/kg ethanol consumed per day. Figure 3 shows the mean values of these calculations and their standard errors. As depicted, there were no significant differences in mean daily ethanol consumption between the two preference tests within any of the groups. Thus, it appears that the preference data presented in Fig. 1 accurately reflects the animals' preferences for ethanol, and was not affected by differences in total fluid consumption between the two tests.

During the drug treatments Group (PCPA) showed a weight loss of 9.3%, Group (PCPA + ETOH) showed a weight loss of 21.1%, Group (ETOH) showed a weight loss of 3.6%, and Group (Veh) showed a weight gain of 4.8%. From these data it appears that the PCPA treatments had

their expected effect on body weight [17], and that the PCPA and ethanol injections were synergistic in this respect.

GENERAL DISCUSSION

In general, the findings of these experiments support the contention of Nachman *et al.* [11] that the reported efficacy of PCPA in reducing the rat's preference for ethanol [2, 6, 8, 9, 10, 17] was probably due to conditioning factors. That is, in Experiment 1 it was found that PCPA caused rats to avoid consuming a metabolically inert saccharin solution under conditions similar to those in which PCPA has been found to produce ethanol avoidance [6, 8, 9, 10, 17], thereby demonstrating that PCPA's capacity to cause consummatory aversions is not specific to ethanol, nor does it depend on an interaction between the metabolism of the avoided substance and the pharmacological effects of PCPA [10], serotonergic or otherwise.

That PCPA's capacity to cause consummatory aversions is the result of conditioning is further supported by the finding in Experiment 2 that PCPA did not cause rats to avoid ethanol when the animals were not allowed to consume ethanol during drug treatments. Since both PCPA and ethanol were administered (Group PCPA + ETOH), it is clear that the pharmacological effects of PCPA and ethanol are not adequate, within themselves, to produce ethanol avoidance. Rather, it appears that the drugs must act while rats have concurrent access to ethanol, as in previous studies [2, 6, 8, 9, 10, 17], if ethanol avoidance is to occur. This requirement affords the opportunity for rats to associate ethanol with the effects of PCPA that may be aversive.

Thus, these findings support the "conditioned taste aversions" interpretation of Nachman *et al.* [11] in that they show taste aversions can be conditioned using the paradigm employed by previous investigators to assess PCPA's effects on ethanol preference, and if the opportunity for such conditioning to occur is eliminated PCPA treatments do not result in diminished ethanol preferences. It has not been demonstrated, however, that PCPA's effect on ethanol preference is due solely to conditioning [11], and such an interpretation appears to be discrepant with several findings.

A major difficulty with an interpretation relying solely on conditioning is the presistence of PCPA induced ethanol aversions after PCPA treatments have been discontinued. While the saccharin aversions conditioned with PCPA in Experiment 1 were found to extinguish within 6 days (Fig. 1), PCPA induced ethanol aversions have been found to require up to 33 days of continuous exposure to ethanol over a period of several months before they dissipate [17]. Part of this discrepancy in extinction rates can be attributed to a palatability difference; saccharin is highly preferred by rats (Fig. 1), whereas ethanol is avoided by rats except when it is presented in low concentrations (Fig. 2). But the magnitude of the difference in which PCPA induced ethanol and saccharin aversions dissipate suggests that some factor other than palatability may be involved.

It has been suggested that the effects of PCPA may somehow interact with ethanol metabolism to make the postingestional effects of ethanol more aversive [10]. Alternatively, perhaps the two drugs interact to make the effects of PCPA more noxious such that simultaneous exposure to PCPA and ethanol, via either ethanol ingestion or ethanol injections, results in more robust conditioning than would occur with PCPA treatments alone. That such an interaction may occur is suggested by the synergistic effects of PCPA and ethanol treatments on body weight loss observed in Experiment 2.

In the latter view, PCPA's capacity to cause rats to avoid consuming ethanol is likely due to the animals associating its noxious effects with the taste of ethanol. A synergistic effect of ethanol on the noxious qualities of PCPA treatments may account for the particularly robust aversions that occur when PCPA is paired with ethanol ingestion. The major difference between this interpretation and that of Myers and coworkers (i.e., [10]) is that it recognizes the dependency of PCPA's capacity to cause ethanol avoidance on conditioning.

As evidence against the possibility that PCPA may cause ethanol aversions via learning, Myers and Martin [8] pointed out that PCPA treatments served to reverse ethanol aversions caused by intracerebral infusions of 5-hydroxytryptophan (5-HTP), the biological precursor of serotonin. One may speculate that, in this case. PCPA may have had an ameliorative action on the apparently aversive effects of 5-HTP infusions. A possible mechanism could be that the inhibition of tryptophan hydroxylase activity by PCPA lowered excessively high 5-HTP levels caused by 5-HTP infusions and, thus, served to restore 5-HTP and/or serotonin levels towards their normal values. In any case, the effects of PCPA probably counteracted those of 5-HTP infusions and, if such effects were beneficial, a reversal of their ethanol avoidance is not surprising. Associating recovery from a variety of noxious states with the consumption of various taste solutions has typically been found to result in rats manifesting enhanced preferences for the taste solutions (see [12]). Thus, again the effects of PCPA on ethanol preferences may have been mediated by conditioning, but in 5-HTP treated rats its beneficial effects may have been associated with ethanol ingestion to result in an enhancement of their preferences for ethanol [8].

It appears, then, that a interpretation based on conditioning can account for most of the reported findings concerning the effects of PCPA on ethanol preferences. The present findings clearly lend support to such an interpretation, but several weaknesses in Experiment 2 prevent using its negative findings as disproof of the "metabolic" interpretation of Myers *et al.* [10].

Perhaps the most serious weakness is the low baseline ethanol preferences shown by most of the groups in Experiment 2 (Fig. 2). Previous findings have suggested that PCPA may differentially effect ethanol preferences such that high drinkers show the most dramatic reductions in ethanol preference [6]. The relatively low ethanol preferences of the animals used in Experiment 2 may have served to obscure some small effect of the PCPA treatments that might have been detectable if the animals were high drinkers. It is clear from the negative findings of Experiment 2, however, that PCPA does not cause the robust ethanol aversions observed elsewhere [2, 6, 8, 9, 10, 17] when the conditions of the experiment preclude the acquisition of conditioned ethanol aversions.

Another weakness of Experiment 2 is that the animals were not allowed to consume ethanol while presumably serotonin deplete. That previous investigators have found the PCPA induced ethanol aversions persist long after serotonin levels should have returned to normal suggests that serotonin depletion is not necessary for the main-

tenance of PCPA induced ethanol aversions [10,17]. It may be, however, that serotonin depletion causes rats to avoid ethanol via some metabolic interaction with ethanol metabolism, and the prolonged duration of PCPA induced ethanol aversions may have been due to the acquisition of conditioned ethanol aversions during the initial period of serotonin depletion.

In conclusion, then, the findings reported here demonstrate that PCPA's efficacy is reducing the rat's preference for ethanol [2, 6, 8, 9, 10, 17] is not solely dependent upon its possible interactions with ethanol metabolism, but that it apparently requires that rats be given access to ethanol during PCPA treatments, thereby supporting the contention of Nachman *et al.* [11] that the effects of PCPA on ethanol self-selection were due to rats acquiring conditioned aversions to ethanol during PCPA treatments. That aversions conditioned to ethanol by PCPA treatments appear to be extremely robust, in comparison to aversions conditioned to saccharin by PCPA (Fig. 1), suggests that perhaps ethanol and PCPA treatments interact synergistically to accentuate their noxious effects.

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