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Effects of Three Monoamine Oxidase Inhibitors on Ethanol Preference in Mice[1]

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SANDERS, B., A. C. COLLINS, D. R. PETERSEN AND B. S. FISH. *Effects of three monoamine oxidase inhibitors on ethanol preference in mice.* PHARMAC. BIOCHEM. BEHAV. 6(3) 319–324, 1977. – These experiments investigated the effects of pargyline, N-[2-(*o*-Chlorophenoxy)-ethyl]-cyclopropylamine (Lilly 51641), and nialamide on voluntary ethanol consumption of C57BL/6J mice. Both pargyline and Lilly 51641 reduced ethanol preference; in contrast, nialamide did not affect preference, despite the fact that it inhibited MAO activity by more than 90%. A subsequent experiment determined that both pargyline and Lilly 51641 produced substantially greater elevations in acetaldehyde levels than did nialamide. It is suggested that increased acetaldehyde is the mechanism responsible for the reduction in ethanol preference observed with pargyline and Lilly 51641.

Alcohol preference MAO inhibitors Acetaldehyde

PREVIOUSLY [15], we reported that pargyline, an inhibitor of monoamine oxidase (MAO), reduced ethanol preference in C57BL/6J mice that were given a choice between 10% ethanol solution and water. Our results suggested that pargyline has relatively specific effects upon mechanisms which mediate alcohol preference, since the drug did not decrease saccharin preference in control animals given saccharin versus water. One possibility is that the effect is mediated through an elevation of brain amines. Serotonin, for example, has frequently been implicated in the control of ethanol intake [12]. However, we also found that pCPA, an inhibitor of serotonin synthesis, did not alter ethanol preference in these animals. An alternative explanation of the pargyline result was suggested by the findings of Cohen *et al.* [2] who reported that pargyline raised levels of acetaldehyde.

The present experiments studied the effects of three MAO inhibitors on ethanol preference in C57BL/6J mice. The first experiment compared the effects of pargyline with those of Lilly 51641. While this experiment was in progress, Cohen *et al.* [1] reported that Lilly 51641 also elevated acetaldehyde levels, whereas another MAO inhibitor, nialamide, had very little effect on acetaldehyde. (For a more complete report of these findings, see Dembiec *et al.* [3].) We therefore carried out a subsequent experiment to determine the effects of nialamide on ethanol preference. A third experiment determined the effects of all three drugs on acetaldehyde levels using doses comparable to those used in the preference studies.

EXPERIMENT 1

The procedures followed in this experiment were similar to those of our initial investigation of the effects of pargyline on ethanol preference [15].

Animals

Animals were 30 male and 30 female C57BL/6J mice, between 45 and 60 days of age at the start of the experiment. Twenty-one of the animals were obtained directly from the Jackson Laboratory; the rest, derived from Jackson Laboratory breeding stock, were obtained from the Institute for Behavioral Genetics. Four animals (three Lilly 51641-treated, and one saline control) died during the treatment period and were replaced.

Method

The experiment consisted of a 12-day pretreatment period, an 8-day drug treatment period, and a 9-day posttreatment period. During the treatment period, mice were given daily intraperitoneal injections of either pargyline, Lilly 51641 or saline. Ten males and 10 females were assigned to each treatment group. Each drug was administered in a saline vehicle in a dose of 50 mg/kg; control animals were injected with .01 ml/g of physiological saline, a volume identical to that given the experimental animals. The pargyline dose was the same as that employed previously [15]. The Lilly 51641 dose was

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determined on the basis of pilot work which indicated a marked reduction in ethanol preference with 50 mg/kg.

Mice were maintained in individual cages and provided with an ad lib ration of solid food (Wayne Sterilizable Lab Blox). They had continual access to two cylinders – one containing tap water, and the other a 10% (v/v) solution of ethanol and tap water. Liquids were presented in inverted 25-ml graduated cylinders with ball-bearing drinking tubes which extended through the cage tops. Cylinders were read daily throughout the experiment. They were rotated every few days according to a predetermined sequence, such that the alcohol solution appeared approximately equally often on the left and right during the pretreatment, treatment, and posttreatment phases of the experiment. Animals were kept on a 12-hr light-dark cycle, with light hours occurring between 8 a.m. and 8 p.m. Drugs were administered between 4 and 6 p.m.

We had previously noted that the effects of pargyline persisted throughout a 10-day posttreatment observation period. Therefore, in this experiment, MAO activity was assessed in 40 subjects one day after the end of the posttreatment period. Thus, whole brain MAO activity was measured 10 days after the last injection of pargyline, Lilly 51641, or saline.

MAO activity was determined using a modification of the assay of Robinson *et al.* [14]. Ten percent brain homogenates were prepared in 0.32 M sucrose, and enzyme activity was estimated for duplicate aliquots of these homogenates. Each incubation tube contained 0.1 ml homogenate, 0.1 ml of a 1 mM $3'^{14}$ C-5-hydroxytryptamine (2.0 μCi per μmole), 0.1 ml of 0.5 M phosphate buffer (pH 7.5), and 0.2 ml water. (5-HT was chosen as a substrate because it has been implicated in alcohol preference, and because Lilly 51641 inhibits its oxidation more than that of phenethylamines [5].) Blank tubes had 0.1 ml of 0.32 M sucrose replacing the brain homogenate. The tubes were incubated in a water bath at 37.5°C for 15 min. Reactions were terminated by placing the tubes in boiling water for 3 min. After coagulated protein was precipitated by centrifugation, the supernatants and two 1-ml washes were placed on a 0.5 × 2.5 cm Amberlite GC-50 column. The Amberlite had been acid and base washed, and the pH was adjusted to 6.5 with 1 M acetic acid. Eluates were collected in scintillation vials, 10 ml of a Triton X-100 toluene scintillation fluid was added, and the radioactivity was assessed in a Beckman LS-133 liquid scintillation counter. Counting efficiency was determined using external standardization. Protein concentration was measured by the biuret method, and data were calculated in terms of μmoles of product formed per mg of protein.

Results

Daily ethanol preference ratios were computed for each subject by dividing the amount of ethanol solution consumed each day by the animal's total fluid intake (ethanol solution + water) for that day. Figure 1 presents the mean preference ratios for mice in the three treatment groups during the pretreatment, treatment, and posttreatment phases of the experiment. The results of three-way analyses of variance (group × sex × day) of these data are reported below. Since preference was expressed as a ratio, the same analyses were also performed on an arcsin transformation of these scores ($\phi = 2$ arcsin $\sqrt{x}$) with virtually identical results.

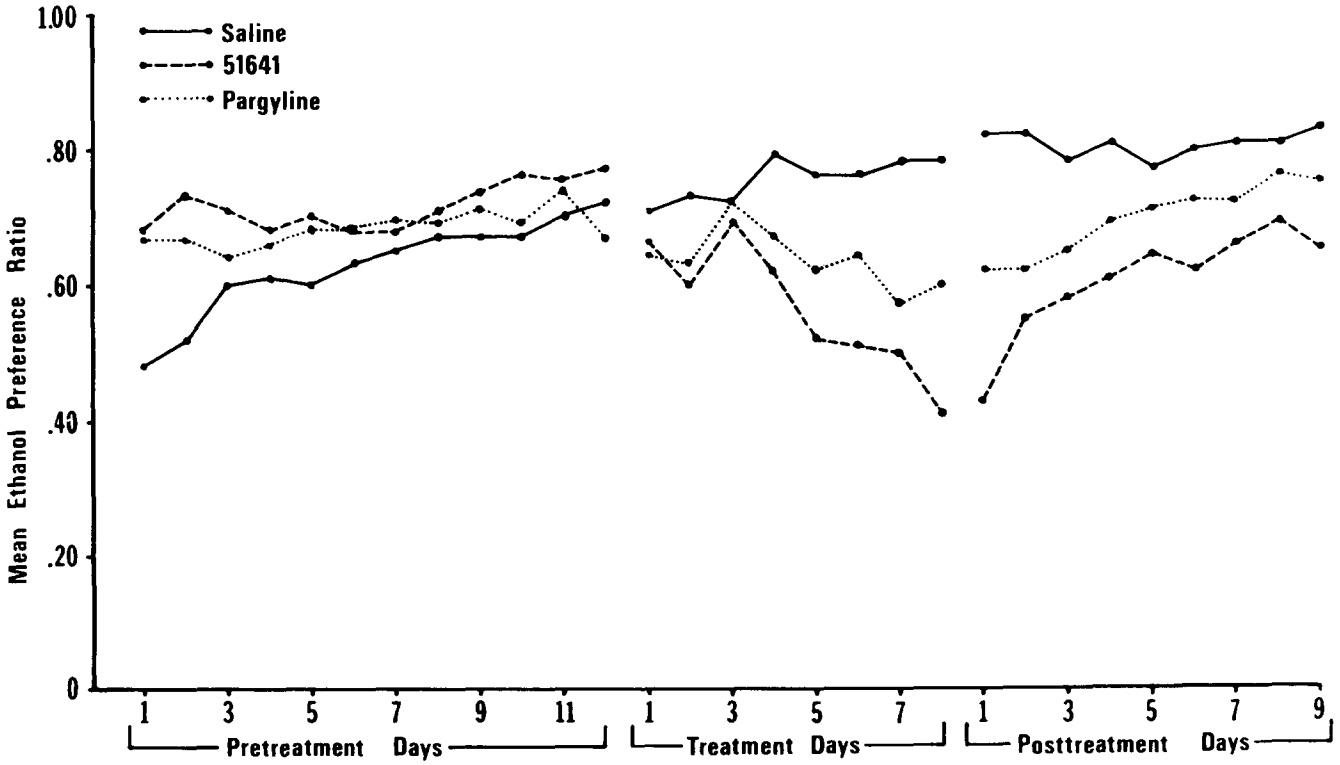

FIG. 1. Mean ethanol preference ratios of the three treatment groups during the pretreatment, treatment, and posttreatment phases of Experiment 1.

Analysis of the pretreatment preference ratios demonstrated that there were no differences in the ethanol preference of animals in the three groups prior to drug treatment. A significant day × sex interaction during this period, $F(11,594) = 3.8$, $p < 001$, reflected the fact that males initially showed a greater preference for ethanol than did females, but that females had higher preference ratios by the end of the 12-day period. After the first two days, the ethanol preference of males remained essentially constant, and that of females increased during the remainder of the period. On the last pretreatment day, preference ratios were significantly higher for females than for males, $t(58) = 2.6$, $p < 0.05$.

Animals treated with pargyline or with Lilly 51641 decreased their preference for ethanol during the period of drug administration, whereas animals injected with saline did not. The group × day interaction was statistically significant, $F(14,378) = 3.2$, $p < 0.001$. Neuman-Keuls tests of this interaction demonstrated that significant differences between the drug-injected groups and the saline-injected control group emerged after four days of drug administration. Females continued to show a greater preference for ethanol than did males, $F(1,54) = 8.2$, $p < 0.01$. A comparison of the ethanol preference ratios of drug-treated groups on the day prior to treatment with those after eight drug treatments demonstrated that Lilly 51641 had a significantly greater effect upon ethanol preference than did an equal dose of pargyline ($t = 2.9$, $p < 0.01$). A sex difference in response to the Lilly compound was also noted. Males showed a 68% reduction in ethanol preference, whereas females showed only a 28% reduction. Subsequent analyses demonstrated that the drug had a more immediate effect upon males than females. The preference of males decreased approximately 28% after a single administration of Lilly 51641 ($t = 2.8$, $p < 0.01$), while females were not significantly affected by one treatment.

The ethanol preference of the drug-injected animals remained depressed beyond the period of drug administration. Analysis of the posttreatment preference ratios revealed a significant effect for group, $F(2,54) = 3.5$, $p < 0.05$) and a significant group × day interaction, $F(16,432) = 2.9$, $p < 0.001$. Neuman-Keuls tests of the interaction demonstrated that the preference ratios of mice that had been injected with Lilly 51641 were lower than those of control animals throughout the 9-day posttreatment period, whereas the difference between the pargyline group and controls was significant only on the first four posttreatment days ($p < 0.01$). Females continued to have higher preference ratios than males, $F(1,54) = 4.9$, $p < 0.05$.

Analysis of the absolute amounts of ethanol solution and of water consumed during the three experimental periods by the mice in the three treatment groups revealed significant group × period interactions, $F(4,108) = 9.6$, $p < 0.01$ for ethanol; $F(4,108) = 7.0$, $p < 0.01$ for water. During the period of drug treatment, both drug-treated groups drank less ethanol than during the pretreatment period, while control animals increased their ethanol consumption. The controls also showed a corresponding decrease in water consumption during the treatment period, whereas the amount of water consumed by the drug-treated animals remained essentially constant. This resulted in a significant drop in total fluid consumption during the period of drug treatment for the treated animals as compared with controls, $f(4,108) = 6.0$, $p < 0.01$. Throughout the experiment, females drank more ethanol solution, $F(1,54) = 5.1$, $p < 0.05$, and less water, $F(1,54) = 4.6$, $p < 0.05$ than did males.

Animals in all three groups maintained body weight during the treatment period. The mean weights on the first day of treatment were 21.5, 21.6 and 21.4 g for mice treated with pargyline, Lilly 51641 and saline, respectively. On the last treatment day the comparable weights were 22.0, 23.1 and 21.7 g.

Brain MAO activity of pargyline- and Lilly 51641-treated animals was significantly less than that of saline control 10 days after the last injection. For pargyline-treated animals, MAO activity was 32% less than that of controls, $t(26) = 3.8$, $p < 0.01$; a 46% reduction was observed in the Lilly 51641-treated animals, $t(22) = 4.3$, $p < 0.01$. Enzyme activities for this experiment are presented in Table 1.

TABLE 1

MAO ACTIVITY 10 DAYS AFTER TREATMENT WITH PARGYLINE, LILLY 51641, OR SALINE

Treatment	μmoles Product Formed (μmoles)/ Protein (mg) $\bar{X}$	SD	N
Pargyline	.0024	.0004	15
Lilly 51641	.0019	.0005	9
Saline	.0035	.0010	13

EXPERIMENT 2

Animals and Method

This experiment assessed the effects of two doses of nialamide (10 mg/kg and 30 mg/kg) on MAO activity and ethanol preference in C57BL/6J mice. Both doses were expected to produce considerable inhibition of MAO. For example, Funderburk [7] reported a 100% reduction in MAO activity in rats after 30 mg/kg of nialamide, and a 90% reduction after 10 mg/kg.

Animals were 20 male mice, 50–59 days old, obtained from the Institute for Behavioral Genetics. Following a 12-day pretreatment period in which baseline levels of ethanol consumption were assessed as in the previous experiment, mice were given daily intraperitoneal injections of nialamide during an 8-day treatment period. Nialamide was dissolved in a slightly acidic saline vehicle and the pH adjusted to neutrality. Seven mice were treated with 10 mg/kg of nialamide, seven with 30 mg/kg, and six with an equivalent volume of saline (0.01 ml/g). Five of the seven animals in the 30 mg/kg nialamide group died. One was found dead on the last treatment day; the others, on the morning after the last treatment day.

Assays for MAO activity, using the same procedure as in Experiment 1, were carried out on all surviving mice on the day after the last injection day. The purpose of these assays was to determine whether nialamide had, in fact, inhibited the activity of MAO. The assays were prompted by a preliminary examination of the preference data, while the experiment was still in progress, which

indicated that treatment with nialamide was not altering ethanol preference.

Results

During the pretreatment period, the mean ethanol preference ratios for the three groups were 0.58, 0.57 and 0.59 for the 10 mg/kg nialamide, 30 mg/kg nialamide and control groups, respectively. The mean preference ratios during the treatment period were 0.48 for the 10 mg/kg nialamide group, 0.49 for the 30 mg/kg group, and 0.52 for the saline-injected controls. The ethanol preference of nialamide-treated animals did not differ significantly from that of controls during the treatment period. A two-way analysis of variance (drug group × day) was also carried out on the preference ratios during the treatment period in order to compare daily changes in the ethanol preference of drug-treated animals with those of controls. The two nialamide groups were combined for this analysis and, in order to equalize the numbers of control and drug-treated animals, data from eight randomly selected control males from the previous experiment were included. This analysis demonstrated that there was no difference in the pattern of ethanol consumption of the two groups during the course of the treatment, nor was there any difference in the average ethanol preference ratios of the groups during this period.

Body weights remained essentially constant during the treatment period. On the first day of treatment, the average weights were 24.5, 23.7 and 25.5 g for animals treated with saline, 10 mg/kg nialamide and 30 mg/kg nialamide, respectively. On the last day of treatment the corresponding weights were 24.3, 24.1 and 25.5 g. Similarly, drug treatment did not appreciably alter fluid intake. For example, the saline, 10 mg/kg and 30 mg/kg nialamide groups drank a mean of 2.36, 2.01 and 2.51 ml of water per day, respectively, during the pretreatment period. During the treatment period, these same animals drank a mean of 2.65, 2.53 and 2.38 ml per day. Ethanol consumption also was not appreciably affected by saline or nialamide treatment.

Although nialamide exerted no influence on ethanol preference, a marked inhibition of MAO activity was seen when it was assessed one day after the last injection. The 10 mg/kg dose caused a 92% reduction in MAO activity; the reduction in the two surviving 30 mg/kg animals was 96%. Enzyme activities for this experiment are presented in Table 2.

TABLE 2

MAO ACTIVITY ONE DAY AFTER TREATMENT WITH NIALAMIDE OR SALINE

Treatment	μmoles Product Formed (μmoles)/ Protein (mg) $\bar{X}$	SD	N
10 mg/kg Nialamide	.0003	.00006	7
30 mg/kg Nialamide	.0001	—	2
Saline	.0039	.00047	6

EXPERIMENT 3

Experiment 3 was carried out to determine whether a differential effect of the three MAO inhibitors on acetaldehyde metabolism might explain the observed effects on preference. Dembiec *et al.* [3] had noted that a 100 mg/kg dose of Lilly 51641 or pargyline caused substantial elevations of blood acetaldehyde following a 4 g/kg ethanol dose, while the same dose of nialamide had very little effect. We investigated the effect of these drugs on adetaldehyde levels using a dose more similar to the ones used in Experiments 1 and 2.

Animals

Animals were 34 male C57BL/6J mice, 50–60 days of age, obtained from the Institute for Behavioral Genetics.

Method

Dembiec *et al.* [3] observed an effect of pargyline, Lilly 51641, and nialamide on acetaldehyde levels when they used a dose (100 mg/kg) considerably greater than those used in our studies. The present experiment assessed the effect of a 40 mg/kg dose of each of the three MAO inhibitors on blood acetaldehyde content following intraperitoneal injection of ethanol. One of the three drugs was injected, in saline, 1.5 hr before administration of 3.0 g/kg ethanol. A 40-μl blood sample was obtained form the retro-orbital sinus 2.5 hr after ethanol injection. It was added to 0.96 ml of a 0.01 mg% isopropyl alcohol solution in a 16 × 100 mm tube. The isopropyl alcohol served as an internal standard. To avoid the possibility of spontaneous acetaldehyde formation in blood hemolysates, the isopropyl alcohol solution contained 25 mM thiourea [4]. Immediately after the blood sample was placed in the tube, the tube was sealed with a rubber stopper and placed on ice until determination of the acetaldehyde content by head-space gas chromatography.

The tubes containing the blood samples were incubated at 65°C for 15 min. A 1.0 ml aliquot of head space gas was injected into a Beckman GC-45 gas chromatograph equipped with a Porapak Q column and flame ionization detector. The inlet temperature was maintained at 150°C, while the column and detector temperatures were 137° and 173°, respectively. Helium served as the carrier gas with a flow rate of 55 ml/min. Hydrogen and air flow rates were 44 and 300 ml/min, respectively. Peak areas were computed with a Hewlett-Packard 3373B integrator and compared with acetaldehyde content. Acetaldehyde content of the standard solutions was determined spectrophotometrically each day by adding yeast alcohol dehydrogenase (.002 units) and 0.35 mM NADH in 40 mM sodium phosphate buffer, pH 7.4. Reactions proceeded to completion, and the concentration of acetaldehyde was calculated by determining the amount of NADH oxidized to NAD as acetaldehyde was reduced to ethanol.

Results

Table 3 presents blood acetaldehyde levels 2.5 hr after injection of ethanol in animals pretreated with pargyline, Lilly 51641, or nialamide. Although all three drugs caused elevations in circulating acetaldehyde levels, a clear difference in the effects of Lilly 51641 and pargyline versus that of nialamide was seen. Lilly 51641 and pargyline increased acetaldehyde levels by factors of 8.4

TABLE 3

BLOOD ACETALDEHYDE LEVELS 2.5 HR AFTER ETHANOL INJECTION IN ANIMALS PRETREATED WITH PARGYLINE, LILLY 51641, OR NIALAMIDE

Treatment (N)	Mean Blood Acetaldehyde ± SE (μg/ml)
Control (16)	1.9 ± 0.5
Pargyline (18)	13.0 ± 1.3*
Lilly (16)	16.1 ± 5.1*
Nialamide (16)	5.0 ± 0.9†

*Significantly different from control at $p<0.01$.
†Significantly different from control at $p<0.05$.

and 6.8, respectively, whereas nialamide caused a much more modest increase. Thus, the two drugs found to decrease ethanol preference produced a much greater increase in acetaldehyde levels than the drug which did not affect preference. It should be pointed out that the dose of Lilly 51641 and pargyline used in this study (40 mg/kg) was less than that used in the preference study (50 mg/kg), whereas the opposite was true for nialamide (for which the maximum dose was 30 mg/kg in the preference experiment).

DISCUSSION

The results of these experiments provide strong evidence that inhibition of MAO *per se* is not responsible for the reduction in alcohol preference produced by pargyline or Lilly 51641. This conclusion is based on the observation that nialamide did not decrease preference, although it did decrease MAO activity by almost 100%. Johnston [10] has suggested that more than one form of MAO exists. These forms, designated A and B, have been shown to differ in substrate specificity and inhibitor sensitivity. Lilly 51641 appears to be relatively specific for MAO-A, whereas pargyline affects MAO-B to a greater extent [6]. Nialamide does not appear to exert any specificity [13]; it inhibits both forms of MAO equally. It should be pointed out that specificity has been observed at doses much lower than those used in the current study. However, even if this specificity does exist at the doses used, it would not be possible to attribute the decreased preference to MAO inhibition, since both Lilly 51641, which inhibits MAO-A, and pargyline, which inhibits MAO-B, decreased alcohol preference, whereas nialamide, which inhibits both A and B, did not influence preference. With regard to substrate specificity, the assay which we utilized to assess MAO inhibition used serotonin as a substrate. Serotonin is believed to be a substrate for MAO-A only [10]. Using serotonin as a substrate, we demonstrated that nialamide, which had no effect on alcohol preference, caused nearly a 100% inhibition of MAO activity. It therefore appears unlikely that inhibition of MAO-A was directly responsible for the decreased ethanol preference produced by Lilly 51641.

Since brain levels of 5-HT are elevated when MAO is inhibited, our nialamide results are relevant to the hypotheses that serotonergic systems are involved in the regulation of ethanol intake [13]. According to this hypothesis, raising 5-HT levels should decrease ethanol preference. Such results have indeed been obtained, for example, following intraventricular injections of 5-HT [9] or introduction of 5-HTP, the metabolic precursor of 5-HT. However, in the present experiments, elevating brain 5-HT levels with nialamide did not alter ethanol preference. Although it is, of course, possible that a necessary minimal level of 5-HT was not achieved with the nialamide treatment, the nialamide result, as well as the inconsistent results which have been obtained with pCPA (see [16]), indicate that further investigation is necessary.

The failure of nialamide to reduce ethanol preference is particularly striking in view of the fact that five of the seven animals injected with 30 mg/kg of the drug died after 7 or 8 days of treatment. This increases the importance of the positive results obtained with pargyline and Lilly 51641, since it suggests that a decrease in ethanol preference under the conditions of our experiments is not produced simply by the general noxiousness of the treatments. Rather, both pargyline and Lilly 51641 appear to have relatively specific effects on ethanol intake control mechanisms.

Dembiec *et al.* [3] observed that Lilly 51641 and pargyline, at 100 mg/kg doses, caused large increases in circulating acetaldehyde levels, whereas nialamide produced a more modest effect. Our results are in excellent agreement with these findings. The conclusion that an elevation in acetaldehyde is the mechanism by which Lilly 51641 and pargyline decrease preference should be viewed with some caution, however. The blood alcohol levels found in Experiment 3 at 2.5 hr after ethanol injection were about 200 mg%. Such a concentration may not be achieved during voluntary consumption. It is interesting to note that Lilly 51641 increased acetaldehyde more than did pargyline and also influenced preference to a greater degree. Nialamide caused a modest increase in acetaldehyde, but did not influence preference at all. This may indicate that some threshold value of acetaldehyde must be exceeded before alcohol consumption is affected.

Although we previously observed that the effects of 8 days of treatment with 50 mg/kg of pargyline persisted throughout a 10-day posttreatment observation period [16], in the present study pargyline continued to inhibit ethanol intake for only 4 days after the treatment period. The effects of Lilly 51641 did persist throughout the 9-day posttreatment period, although animals gradually increased their consumption of ethanol during this time. Biochemical assays indicated that MAO activity was still inhibited in both drug-treated groups at the end of the posttreatment period. The activity of the enzyme in the pargyline-injected group was slightly greater than in the group treated with the Lilly compound. Since our results suggest that acetaldehyde may be responsible for the reduction in ethanol preference produced by these two drugs, it would be expected that levels of this substance might exhibit a closer relation to ethanol preference than MAO activity both during treatment and after treatment. We are currently exploring the time course of MAO inhibition and of acetaldehyde elevation following treatment with MAO inhibitors.

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