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Evidence Against a Biphasic Effect of Acetaldehyde on Voluntary Ethanol Consumption in Rats[1]

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ERIKSSON, C. J. P. AND R. A. DEITRICH. *Evidence against a biphasic effect of acetaldehyde on voluntary ethanol consumption in rats.* PHARMAC. BIOCHEM. BEHAV. **13**: Suppl. 1,291–296, 1980.—A group of 27 male Long-Evans rats was given a 2 week period of free-choice ethanol and consumed 1.26 ± 1.27 g/kg/day (mean ± SD). The animals were then divided into 3 groups. One group received the aldehyde dehydrogenase inhibitor, cyanamide, in their diet and an oral ethanol dose of 2 g/kg for 5 days. Another group received only the oral ethanol dose and the third, control, group received no treatment during these days. After the forced cyanamide and/or forced ethanol treatment, all of the rats were returned to the choice situation. Voluntary ethanol consumption was then followed for 2 months, during which time the control rats steadily increased their ethanol intake to 3.6 ± 2.1 g/kg/day (mean ± SD of last week's consumption). The cyanamide treatment caused a transient (3–4 day) decrease in the ethanol intake, after which the consumption increased to 3.7 ± 2.9 g/kg/day. Consumption by the forced ethanol group (5.4 ± 2.0 g/kg/day) was significantly greater ($p<0.05$) than that by the other rats. The present results do not favor a physiological role for acetaldehyde-induced formation of alkaloids in increasing voluntary ethanol consumption, but do support the notion of an acetaldehyde-mediated aversive effect on ethanol drinking.

Ethanol Acetaldehyde Ethanol drinking Voluntary ethanol consumption

THE presence of elevated acetaldehyde (AcH) concentrations during ethanol ingestion is a well-known aversive factor in ethanol drinking behavior in experimental animals [11, 13, 35, 36, 38]. "Peripheral" toxicity [13] and inhibition of brain aldehyde dehydrogenase (ALDH)-mediated reactions [11,13] have been proposed as possible mechanisms. Human alcoholism has been treated with the ALDH inhibitor disulfiram [18,26] and is successful presumably because of the AcH-induced aversion to ethanol. Moreover, it seems that the inherent "sensitivity" to ethanol which is probably caused by elevated AcH [16, 22, 28, 48] due to deficient ALDH [20,21] in many orientals [29, 46–48], may also reduce voluntary ethanol intake [16, 47, 48].

In contrast to the aversive effects of AcH on ethanol consumption, there are observations which indicate that intraventricularly injected AcH reinforces ethanol drinking in rats [1,32]. In addition, the intraventricular injection of tetrahydroisoquinoline (TIQ)-alkaloids, condensation products of catecholamines with AcH or biogenic aldehydes [5], has been found to initiate excessive drinking in rats [27, 30, 31]. Other studies, however, have failed to replicate these results [4], and still others [10] have been only partially successful in replication attempts. Observations of elevated AcH levels in alcoholics [17, 24, 44] or their relatives [37] and in the Ojibwa Indians with high ethanol consumption [34] suggest that AcH also may play a role in promoting ethanol drinking in humans.

A biphasic model was recently suggested in an attempt to explain the seemingly contradictory observations described above [13]. According to this model, AcH could have both an aversive and a reinforcing effect, the combination of which would determine the total effect of AcH on ethanol drinking behavior. The present study has been designed to test the possibility of a biphasic effect of AcH.

Baseline drinking behavior was recorded for a group of rats. Elevated AcH concentrations were then induced in one group of animals during a 5-day period of ethanol treatment by the use of the ALDH inhibitor cyanamide; thereafter voluntary ethanol consumption was followed for another 2 months.

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TABLE 1

BLOOD ACETALDEHYDE CONCENTRATION*

	Control Group (n=8)	Ethanol Group (n=9)	Cyanamide Group (n=10)
Before cyanamide treatment, 1 hour after ethanol intubation (day 26)	22 ± 15	23 ± 20	20 ± 14
During cyanamide treatment, 1 hour after ethanol intubation			
Day 28		22 ± 14	1170 ± 483
Day 30		7 ± 11	859 ± 516
Day 32		36 ± 20	926 ± 581
During cyanamide treatment, before ethanol intubation (day 31)†	1 ± 3	1 ± 3	11 ± 4
After cyanamide treatment, 1 hour after ethanol intubation (day 43)	31 ± 24	35 ± 33	23 ± 19

*μM ± SD.
†No detectable ethanol.
Ethanol dose was 2 g/kg; see legends of Figures 1–3. Data for "Cyanamide Group" represents mean for animals in all dose groups (see Table 2).

TABLE 2

EFFECT OF CALCIUM CYANAMIDE IN THE DIET ON BLOOD ACETALDEHYDE LEVELS

Calcium Cyanamide			Blood Acetaldehyde
mg/kg Diet	(n)	mg/kg Body Wt. per Day	μM (Av. 3 Days)
0	(10)	0	20 ± 14
50	(2)	3.05	309
100	(2)	4.65	825
200	(2)	8.90	1120
300	(2)	12.95	1250
400	(2)	13.75	1530

Calcium cyanamide was mixed with the diet in the amounts indicated and the diet was offered from day 27 to 32. Ethanol, 2 g/kg, was given by intubation. Blood for determination of acetaldehyde levels was taken 1 hour after intubation.
The dose of cyanamide was calculated from the body weight and food intake.

METHOD

Animals

Male Long-Evans rats (n=27), purchased from Simonsen, Gilroy, CA were used. The animals weighed 294–383 g at the start of the experiments. Standard diet (Purina lab chow) was provided ad lib.

General Procedure

On day 0 the animals were put into individual cages. Food and water consumption were then measured for an 11-day control period in order to ensure normal nutrition. After this period all rats were offered free choice (2 bottles) between 10% ethanol (v/v in tap water) and tap water for 14 days. The bottles were randomly rotated in order to avoid position preference [19]. On day 26, the rats were intubated with 10% (w/v) ethanol (2 g/kg) and blood (tail) AcH determined 1 hour after ethanol administration as previously described [14].

On day 27 the rats were divided into 3 groups which were matched with regard to body weight, nutritional intake, voluntary ethanol consumption, and blood AcH concentration as determined on day 26. The groups will hereafter be called the control, ethanol and cyanamide groups. The animals belonging to the ethanol and cyanamide groups received daily ethanol (10%, w/v), 2 g/kg, by intubation in the morning of days 28 to 32. In addition, the cyanamide group received cyanamide, as calcium carbimide (Dipsan® from Lederle, Montreal), which was ground into the diet in doses ranging from 50 to 400 mg/kg diet. Blood AcH was determined 1 hour after the ethanol intubation on days 28, 30 and 32. Once (day 31) blood AcH was measured before the ethanol intubation. The control animals received no treatment durings days 28 to 32.

On day 32 the cyanamide diet was changed to normal diet. The rats from all groups were now put on the free choice situation for the next 10 days (days 33–42). On day 43 all animals were intubated with ethanol (2 g/kg) and blood AcH was determined 1 hour after the ethanol administration. On day 44, the control animals were put back on the free choice and kept so for the next 37 days (days 45–81). The rats belonging to the ethanol and cyanamide groups were also kept on the same free choice situation except during days 45–47 and 59–66 during which 10% (v/v) ethanol was the only fluid available.

RESULTS

No differences in body weight between the different groups were observed at any time of the experiment. All animals gained weight during the whole experimental period except during days 25–32, during which the animals lost 5–7% of their body weight. The mean body weights from day 0 to day 78 were 333 to 424 g (controls), 329 to 436 g (ethanol group), and 342 to 439 g (cyanamide group).

Table 1 demonstrates that the cyanamide treatment greatly elevated the blood AcH concentrations during the days of ethanol intubation (28–32). This effect was dose-dependent with regard to cyanamide. The average AcH concentrations during this period are illustrated in Table 2. There was no tendency with any cyanamide dose for the AcH concentration to increase with the duration of treatment. On day 31 significant AcH levels (Table 1) were observed in the blood of the cyanamide animals before the daily ethanol intubation. No relationship between the cyanamide dose and the magnitude of the "endogenous" AcH concentration was observed.

The reason for illustrating both individual (Figs. 1–3) and average (Fig. 4) voluntary ethanol consumption is that there are large individual variations in ethanol drinking behavior in these rats. Figures 1–3 demonstrate that each group of rats included both "nondrinking" individuals and rats which consumed ≥3 g/kg during the 2-week control drinking period (days 12–25). A gradual increase in ethanol consumption with time in all groups may be observed (Fig. 4) as a general pattern. This increase was largest in the ethanol group, in which none of the animals stayed nondrinking throughout

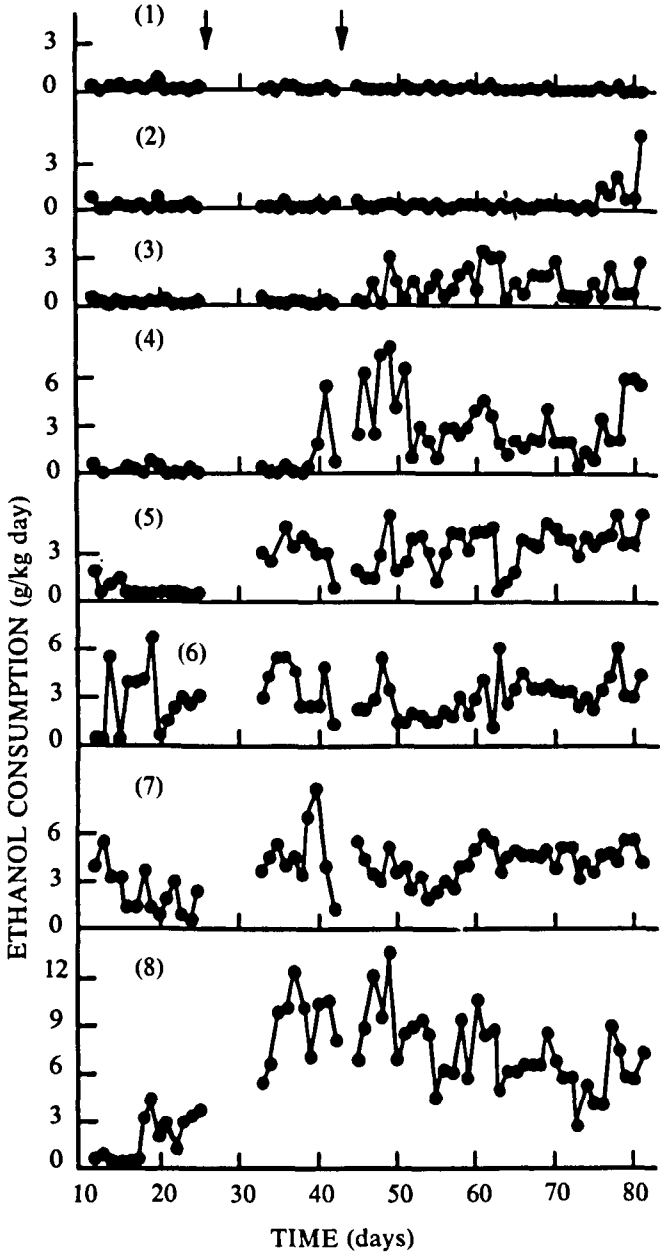

FIG. 1. Individual voluntary ethanol consumption scores (control group). Ethanol (2 g/kg) was intubated twice as indicated by the arrows.

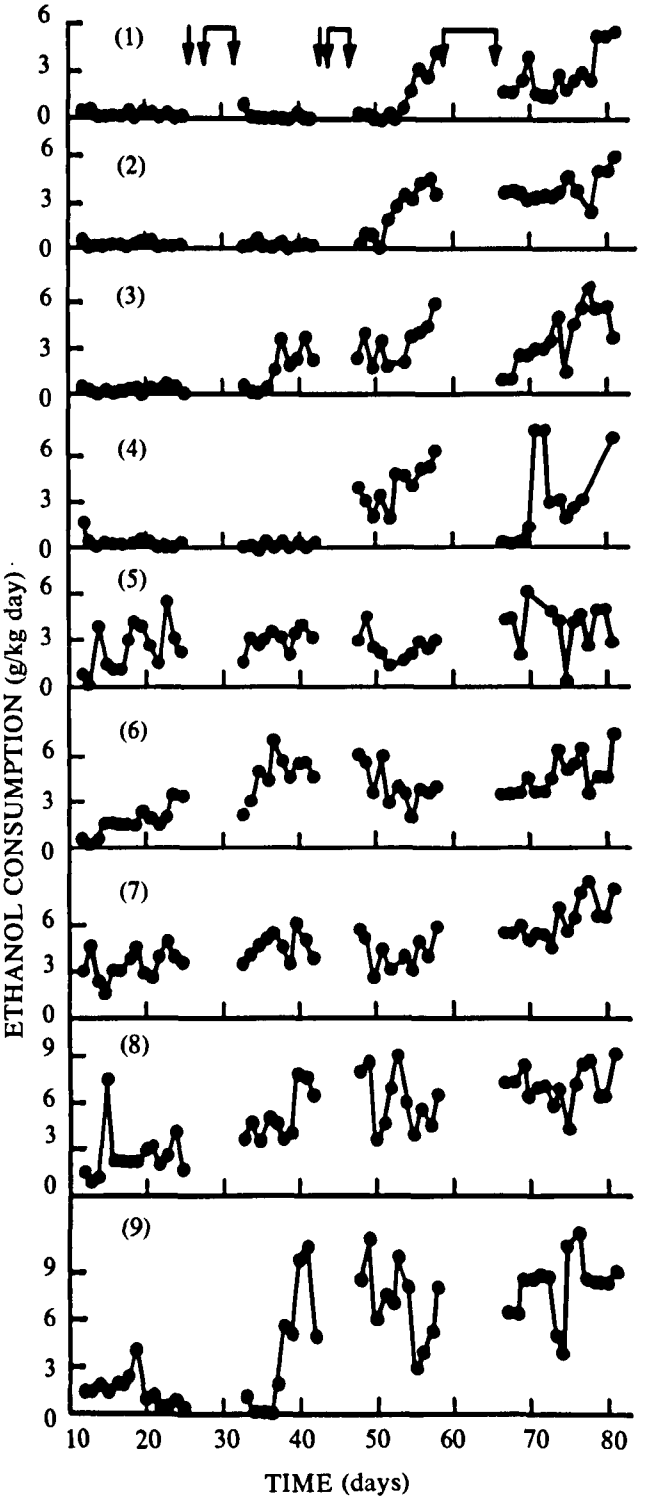

FIG. 2. Individual voluntary ethanol consumption scores (ethanol group). Ethanol (2 g/kg) was intubated 7 times (days 26, 28–32, 43). Ethanol (10%, v/v) was the sole fluid on days 44–47 and 59–66.

the experiment. The cyanamide and control animals similarly increased their drinking, except for a 3–4 day transient period after the cyanamide treatment when the cyanamide animals consumed less ethanol (Fig. 4). As may be observed in Fig. 3, 3 of the 4 rats which drank significant amounts of ethanol during the control drinking period (rats 2a, 4b, and 8d) completely stopped drinking for 3–4 days. The fourth rat (6c) on which the cyanamide had no effect, was the animal with the highest of all voluntary ethanol consumption both before and after the treatment period.

DISCUSSION

Blood Acetaldehyde

The effect of cyanamide on blood AcH levels during ethanol intoxication fits well with earlier data on rats [2, 25,

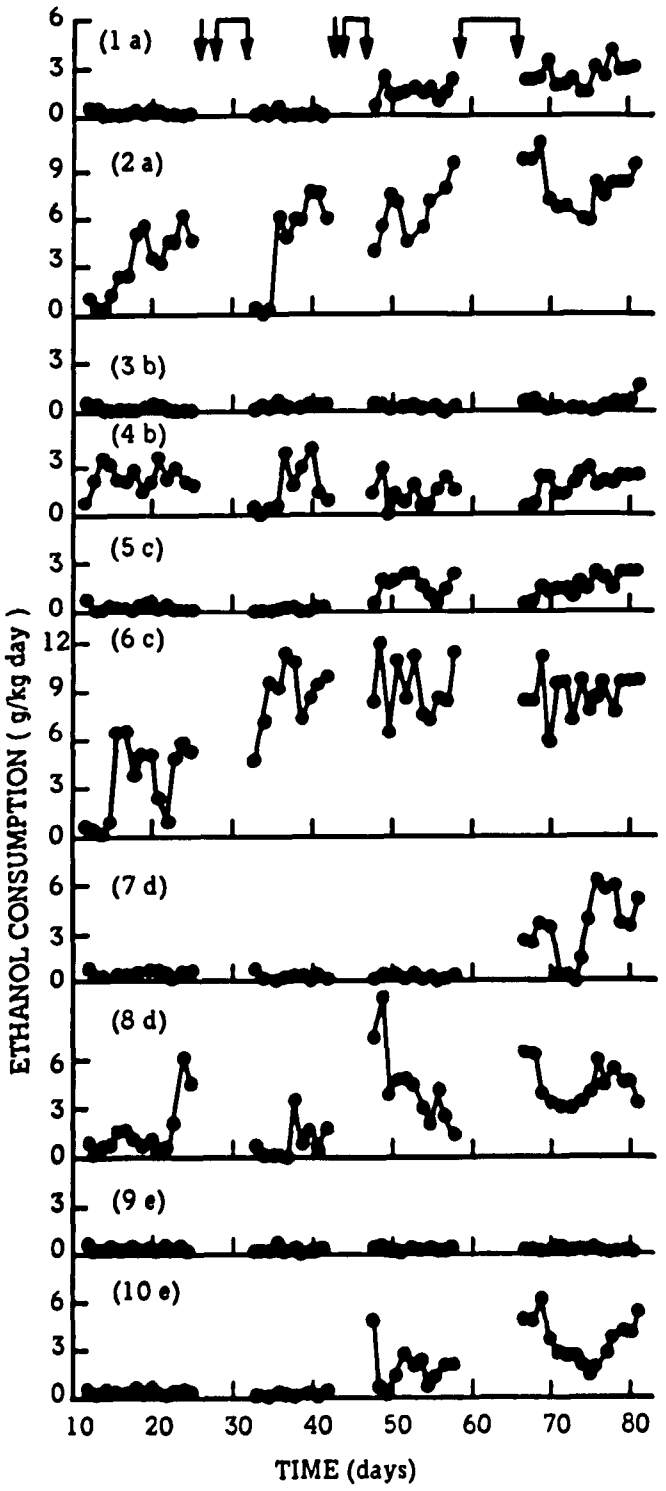

FIG. 3. Individual voluntary ethanol consumption scores (cyanamide group). Ethanol treatment as for the ethanol group (Fig. 2). Calcium cyanamide was in the diet (a: 50 mg/kg of diet, b: 100 mg, c: 200 mg, d: 300 mg, e: 400 mg) on days 27–32.

45]. The lack of a cumulative effect of the lower cyanamide doses on the AcH levels most likely indicates that the inhibition of ALDH by cyanamide and/or its *in vivo* derivative(s) is easily reversible in contrast to the irreversible inhibition by disulfiram [8,23]. Another possibility is that the inhibited enzyme has a rapid turnover, but this seems unlikely. The occurrence of endogenous AcH (11 ± 4 μM, Table 1) during cyanamide treatment should also be noted. Similar observations but higher AcH concentrations (18–116 μM) during cyanamide, disulfiram or pargyline treatment have been reported earlier [3,43], but these reports have been questioned [6], mostly because of the difficulty with blood AcH determinations. Whether the endogenous AcH levels observed in the present study reflect inhibited endogenous AcH metabolism, or release of remaining bound AcH derived from previously intubated ethanol, should be the target for further studies.

The high blood AcH levels reported in Table 2 require some comment. One can calculate the AcH level at equilibrium of the alcohol dehydrogenase (ADH) reaction [7]. Taking the equilibrium constant of 2.0×10^{-4} M for ADH at pH 7.4, an ethanol concentration of 50 mM and a NAD/NADH ratio of 200, an AcH concentration of about 200 μM should bring the ADH reaction to equilibrium. Thus the blood AcH levels of over 1500 μM (Table 2) should completely inhibit ethanol oxidation via ADH and demand that AcH arise from some pathway other than ADH. It would be possible to achieve high levels of AcH if its oxidation to acetate were markedly slowed by the cyanamide treatment. Eventually however, the levels of AcH should drop to the equilibrium level, unless the formation by non-ADH pathways is faster than reduction of AcH to ethanol.

These results indicate that administration of cyanamide in the diet is an efficient procedure by which AcH metabolism may be inhibited. Previous work, in which pargyline was used to almost completely inhibit rat liver mitochondrial ALDH, resulted in blood AcH levels of 440 μM, 150 minutes after a dose of 2.5 g/kg of ethanol [33]. These results could also be taken to indicate that cyanamide is an effective *in vivo* inhibitor of most if not all ALDH isozymes in liver, as previously found in mice [9]. In that study the ED_{50} for inhibition of mouse liver ALDH activity by cyanamide was 8 mg/kg. That dose corresponds to a dose of 15 mg/kg of calcium cyanamide.

Acetaldehyde and Ethanol Consumption

The expected pattern of a biphasic action of AcH on drinking includes a decrease immediately following the conclusion of cyanamide treatment, followed by a subsequent increase in the ethanol drinking by the cyanamide group compared to the other animals. The decrease was observed in the present study (except in one rat with consistently high ethanol consumption). This decreased ethanol consumption is in accordance with a recent study demonstrating cyanamide-induced inhibition of voluntary ethanol consumption [40]. The effect was suggested to relate to a direct inhibitory effect of cyanamide on brain ALDH, which also would be in accordance with the possible mechanism of AcH-mediated brain ALDH inhibition reducing ethanol drinking [11,13]. An earlier study demonstrating little effect by cyanamide on drinking [2] may be explained by the technique of using drinking on alternate days and selecting the animals with a stable but relatively high baseline drinking. Thus, those animals may have been similar to the one animal

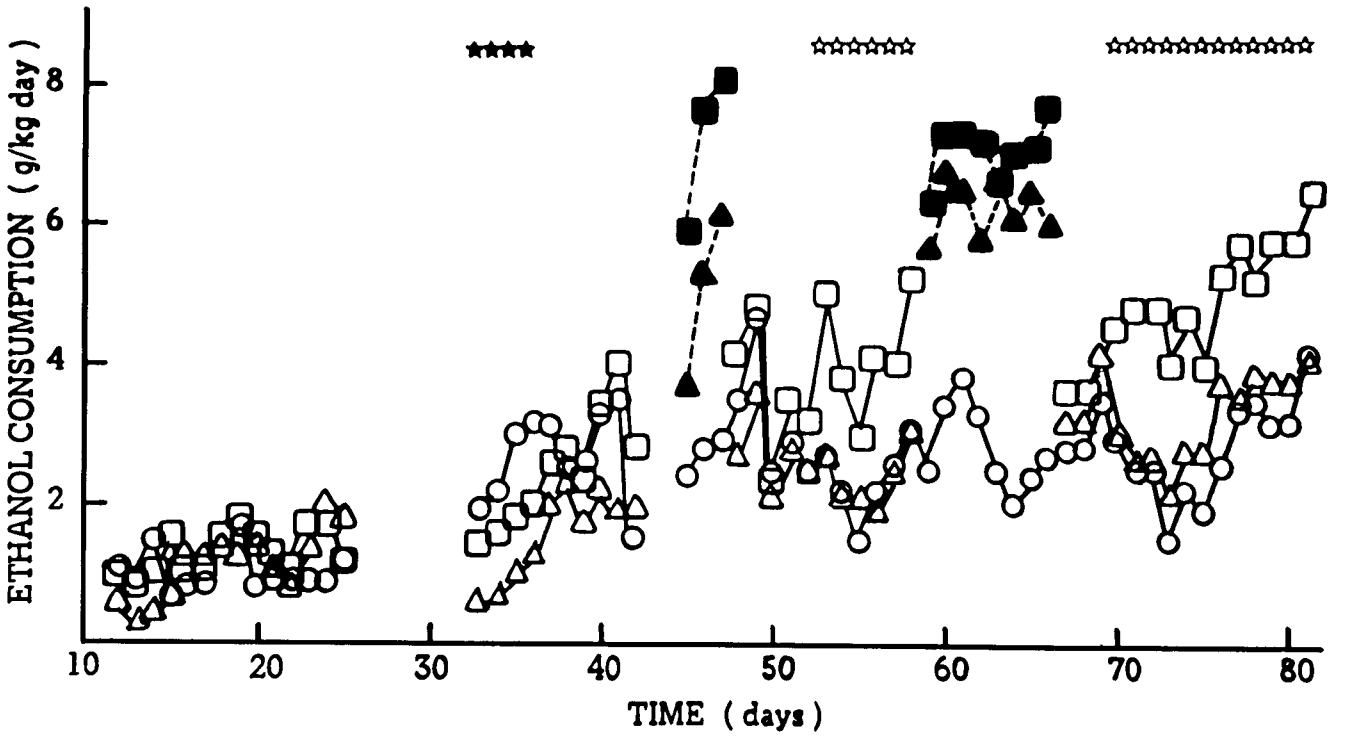

FIG. 4. Average voluntary ethanol consumption. Control group: open circle, ethanol group: open square, cyanamide group: open triangle. Ethanol (10% v/v) as sole fluid: solid symbols. Significant (Student's t-test, $p<0.05$) group differences: cyanamide versus ethanol + control group: shaded star, ethanol versus cyanamide + control group: open diamond.

in the present study with the highest ethanol consumption whose drinking was not effected by cyanamide (Fig. 3). This would suggest that there are animals with a drinking motivation strong enough to overcome the temporary aversive effect of AcH and/or brain ALDH inhibition. This points up the necessity for careful testing of animals in voluntary drinking experiments and/or the use of more homogenous animals such as inbred strains.

In contrast to the hypothesis of the biphasic action of AcH, no "overshoot" in ethanol consumption was observed after the aversive period. In fact, the same gradual average increase in voluntary ethanol consumption as with the control animals was observed in the cyanamide-treated rats. Such a time- (or age-) dependent increase in voluntary ethanol consumption has been observed previously [15,41]. The absence of an increased drinking as an "after" effect of the cyanamide treatment cannot be explained by the possibility that AcH did not penetrate into the brain, since the blood AcH concentrations in the cyanamide animals far exceeded the level necessary to exceed the metabolic "capacity of brain", which is about 200 μM for rats [12,42]. The effect of forced ethanol intake to increase voluntary ethanol consumption (ethanol compared with the cyanamide and control groups) is also well-known [39]. It is interesting to note that the cyanamide-treated rats consumed the same as controls; thus cyanamide treatment blocked the effect of forced ethanol on drinking.

Several methodological factors may explain the lack of a biphasic effect of the elevated AcH on the voluntary ethanol consumption in the present experiment. Dose and time factors for the cyanamide treatment might have either been ineffective in producing TIQ-alkaloids in the correct amount or for a sufficiently long period to produce the previously reported [27] long-lasting excessive ethanol drinking. With regard to the use of ALDH inhibitors in the treatment of human alcoholism it may be concluded that the present results suggest these inhibitors may be used without incurring additional addictive liability.

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