Acetaldehyde-reinforcing effects: differences in low-alcohol-drinking (UChA) and high-alcohol-drinking (UChB) rats

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Abstract

It has been suggested that acetaldehyde has a biphasic effect on voluntary alcohol consumption. At low brain concentration, it might exert reinforcing effects, whereas high acetaldehyde levels would be predominantly aversive. The objective of the current study was to compare the effect of an intraperitoneal dose of acetaldehyde (50 mg/kg) in high-alcohol-drinking (UChB) and low-alcohol-drinking (UChA) rat lines, which differ in the activity of the brain mitochondrial class 2 aldehyde dehydrogenase (ALDH2) as a consequence of differences in their *ALDH2* genotypes. A classical place-conditioning procedure was used to determine the reinforcing or aversive (or both) effects of acetaldehyde in ethanol-naive UChB and UChA rats. Environmental cues were paired with an intraperitoneal 50-mg/kg injection of acetaldehyde. On 10 consecutive days, each rat received one place conditioning per day; the acetaldehyde-pairing was alternated with saline-pairing. Results showed that conditioning with the 50-mg/kg dose of acetaldehyde induced place preference in UChB rats and place aversion in UChA rats. In a second experiment, UChB and UChA rats, pretested for ethanol preference, were injected with one 50-mg/kg dose of acetaldehyde or saline and tested for their voluntary ethanol consumption during 4 weeks. Results showed that the acetaldehyde dose induced a persistent and long-lasting enhancement of ethanol intake in UChB rats, but not in UChA rats. These results, together with the finding that after administration of a 50-mg/kg dose of acetaldehyde cerebral venous blood acetaldehyde levels in UChA rats were consistently higher than levels in UChB rats, support the suggestion that differential acetaldehyde levels, differential brain ALDH2 activity, or both were responsible for the different effects of acetaldehyde in the two rat lines.

Keywords: Acetaldehyde reinforcement; Conditioned place preference; Conditioned place aversion; Alcohol preference; Brain ALDH2 activity

1. Introduction

It has been postulated, over the past 30 years, that acetaldehyde, the first metabolite of ethanol, is a mediator of actions of ethanol in the brain. It is generally accepted that the enzyme aldehyde dehydrogenase (ALDH), which is located in the mitochondrial matrix and that presents a low Michaelis–Menten constant (K_m) for acetaldehyde [i.e., mitochondrial class 2 aldehyde dehydrogenase (ALDH2)], plays the major role in the oxidation of acetaldehyde (Eriksson et al., 1975). With regard to the effects of acetaldehyde on voluntary alcohol consumption, there is evidence supporting the suggestion that acetaldehyde has a biphasic effect. On one hand, there is general agreement that elevated blood acetaldehyde concentrations are aversive and are the basis for treating alcohol-dependent persons with disulfiram (Antabuse), an inhibitor of ALDH. Furthermore, in some human beings, a point mutation (*ALDH2*2*) in the encoding gene for the *ALDH2* (Yoshida et al., 1984) results in a decreased capacity to oxidize acetaldehyde and leads to its accumulation in the blood after alcohol intake (Agarwal & Goedde, 1989; Teng, 1981). People who are deficient in ALDH2 have been shown to consume less alcohol than consumed by those who are not deficient in ALDH2, because acetaldehyde accumulation results in aversive physiologic reactions (Peng et al., 1999; Tu & Israel, 1995).

In contrast, results of studies, showing that acetaldehyde is easily self-administered into the ventricular system of the brain (Brown et al., 1979) and into the ventral tegmental area (McBride et al., 2002) by laboratory rats, seem to indicate that acetaldehyde possesses reinforcing properties. In support of this notion, it has been shown that rats would display a positive place conditioning after intracerebroventricular infusions of acetaldehyde (Smith et al., 1984). However, the observation that the propensity of rats to self-administer acetaldehyde was related to their propensity to drink ethanol solutions was the first indication that acetaldehyde may play a mediational role in voluntary alcohol consumption (Brown et al., 1980).

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It has been suggested that an important factor in determining whether acetaldehyde exerts either reinforcing or aversive effects may be its brain concentration. At low concentrations, acetaldehyde might exert reinforcing effects, whereas further acetaldehyde accumulation, above a specific upper limit, would be predominantly aversive (Hunt, 1996).

Rat lines, developed at the University of Chile (Mardones & Segovia-Riquelme, 1983), consume ethanol at either low [0.1–2 g/kg/day: low-alcohol-drinking (UChA)] or high [4–7 g/kg/day: high-alcohol-drinking (UChB)] levels with free choice between 10% [volume/volume (vol./vol.)] ethanol solution and water. We have shown previously that intact brain mitochondria isolated from UChA rats, compared with findings for UChB rats, display a lower ALDH2 activity as a consequence of a lower affinity for its co-factor, the oxidized form of nicotinamide adenine dinucleotide (NAD^+) (Quintanilla & Tampier, 1995). Results of this study indicated that the K_m for NAD^+ is fivefold higher in the UChA animals (96–126 μM) than in the UChB animals (21–23 μM), without changes in the maximum velocity (V_{max}). Results of a recent study have shown that such K_m differences were due to genetic differences in the coding of ALDH2 (Sapag et al., 2003).

UChA and UChB animals do not display differences in blood acetaldehyde levels after ethanol administration (Tampier et al., 1996). This is unlike what is observed in human beings with the (glutamic acid 487 lysine) mutation, which renders ALDH2 virtually inactive, leading to marked elevations in blood acetaldehyde levels after alcohol intake (Mizoi et al., 1983; Yoshida et al., 1985). However, UChA rats, when compared with UChB rats, display a slower rate of elimination of exogenously administered acetaldehyde, supporting the suggestion that acetaldehyde elimination in tissues with low levels of NAD^+ such as brain (Quintanilla et al., 2002; Tampier et al., 1999) may influence tissue acetaldehyde disposition. Thus, in UChA rats, in which brain ALDH2 activity is lower than the activity in UChB rats, acetaldehyde accumulates to a great extent and possibly would be predominantly aversive. Consistent with this hypothesis, it has been shown that UChA rats exhibit a marked aversion to an intraperitoneal dose of acetaldehyde (50, 100, or 150 mg/kg), whereas UChB rats do not exhibit aversion to any dose of acetaldehyde (Quintanilla et al., 2002). If brain acetaldehyde concentration is an important factor in determining whether acetaldehyde exerts either reinforcing or aversive effects, UChA and UChB rats may differ also in their sensitivity to the reinforcing properties of acetaldehyde.

The aim of the current study was to compare directly the reinforcing properties of an intraperitoneal dose of acetaldehyde (50 mg/kg) in UChA and UChB rats with the use of the conditioned place preference method. In addition, the possibility that acetaldehyde may act as a mediator of alcohol consumption was investigated by determining whether an intraperitoneal dose of acetaldehyde (50 mg/kg) would alter the self-selection of ethanol in UChA and UChB rats.

2. Materials and methods

2.1. Place conditioning with acetaldehyde

2.1.1. Animals

Fifteen, ethanol-naive (not pretested for ethanol preference), male rats of each line (UChA and UChB), each weighing between 250 and 275 g, were housed individually in a room controlled for constant temperature and humidity and a 12-h light/12-h dark cycle. Food and water were available ad libitum throughout the experiment in the home cage. The care and use of laboratory animals, as well as all procedures involving animal experiments reported in this article, were in accord with regulations of the Institutional Animal Care and Use Committee of the University of Chile.

2.1.2. Procedure

In place conditioning, subjects are treated by explicitly pairing distinctive neutral environmental cues with administration of acetaldehyde stimulus. The subjects are later given an opportunity to spend time in the presence of cues paired with acetaldehyde stimulus. The subjects approach, avoid, or act neutrally toward the cues, depending on the nature of the unconditioned stimulus. In general, pairing cues with appetitive reinforcers produces approach to the cues, whereas pairing with aversive reinforcers or punishing stimuli produces avoidance of the cues. The acetaldehyde-rewarding effects were determined by using the conditioned place preference method, as described previously (Smith et al., 1984).

The experimental chamber consisted of a narrow wooden box ($60 \times 25 \times 30$ cm^2), which was divided in half. The walls of one side of the box were painted white with a wire mesh covering wooden floor, whereas the walls of the opposite side were painted black with a plain wooden black floor. It was possible to separate the two compartments by a guillotine door, constructed with walls similar to those of each side of the box, and place it in the middle of the chamber. The entire apparatus was contained within a ventilated, sound-attenuating, and light-illuminated room.

Rats were given access to the entire chamber, with the guillotine door removed, for 5 min once per day for 3 days. The amount of time spent on each side was recorded, and the "preferred side" of each animal was assessed. A side was considered "preferred" when the mean time spent for the last 2 days in this side was more than 80% (>240 s) of the total time. There was no line difference in the preferred side, because 93% of UChA and 93% of UChB rats preferred the black side of the chamber. The observer did not know the experimental procedure undertaken on the rat under investigation. After this preexposure period, the nonpreferred side of each animal was identified. These data served to confine the animals injected with acetaldehyde to this side of the chamber during conditioning trials.

Five conditioning trials were given every second day, during which each rat was injected intraperitoneally with a dose of acetaldehyde of 50 mg/kg in a 1.6-g% [weight/

volume (wt./vol.)] concentration and placed in the nonpreferred side of the box for 15 min to allow the association between the acute effects of the conditioning drug and the environmental cues. On intervening days, each rat received an intraperitoneal dose of saline (NaCl 0.9%) and was placed in the preferred side for 15 min.

The testing session was conducted on the day after the last conditioning session. The rats were allowed to run freely in the entire apparatus with the guillotine door removed for 15 min per day on two consecutive days. The time spent in each side was recorded under a blinded procedure; that is, the observer did not know the experimental procedure undertaken on the rat under investigation.

2.2. *Effect of one dose of acetaldehyde on voluntary ethanol consumption*

2.2.1. *Animals*

Thirty male UChA and 30 male UChB rats, each weighing between 180 and 200 g and not tested for ethanol preference at the start of the experiment, were used.

2.2.2. *Establishing voluntary ethanol consumption*

The rats were housed individually in a temperature- and humidity-controlled room, with a 12-h light/12-h dark cycle, and were given free access to a 10% (vol./vol.) ethanol solution, water, and food for 8 weeks. Ethanol and water consumption were recorded every day. Ethanol intake was calculated for each rat as the mean amount of ethanol consumed during the last 4 weeks of preference testing and was expressed as grams of ethanol per kilogram of body weight per day.

2.2.3. *Procedure*

After the determination of ethanol consumption, the animals of each line were randomly divided into two groups. One group was injected intraperitoneally with one 50-mg/kg dose of acetaldehyde, and the other group was injected with an equal volume of saline. Acetaldehyde was injected as a 1.6-g% (wt./vol.) solution prepared from 99% acetaldehyde and sterile saline. The rats were immediately returned to their home cages with free choice between 10% (vol./vol.) ethanol solution and water for 4 weeks. Ethanol and water consumption were recorded every day.

2.3. *Determining cerebral blood acetaldehyde concentration*

Cerebral blood acetaldehyde levels were determined in different groups of ethanol-naive male UChA ($n = 5$) and UChB ($n = 5$) rats. After each rat was anesthetized with a 50-mg/kg dose of sodium pentobarbital, administered intraperitoneally (Cassel et al., 1987; Dewey & West, 1985; Paez & Myers, 1989), it was secured to a holder and a small hole was made in the skull. Next, 0.1-ml samples of blood were obtained from the superior sagittal blood sinus at 2, 5, and 10 min after an intraperitoneal injection of acetaldehyde (50 mg/kg). Acetaldehyde was injected as a 1.6-g% (wt./vol.) solution prepared from 99% acetaldehyde and sterile saline. In each sample, acetaldehyde was determined by head-space gas chromatography according to Eriksson et al. (1977). An ethanol peak higher than 1 mM (the gas chromatograph detection limit for ethanol) was not found in any blood sample chromatograms, indicating that acetaldehyde was not reduced to a significant amount of ethanol by the alcohol dehydrogenase system.

2.4. *Statistical analyses*

The results were expressed as mean (± S.E.M.). Data obtained for place conditioning, voluntary ethanol consumption, and acetaldehyde concentration in cerebral venous blood were analyzed by using a two-way analysis of variance (ANOVA) with line and treatment as factors. Post hoc comparisons of differences between group means were made by using Newman–Keuls tests.

3. Results

3.1. *Effect of acetaldehyde conditionings on stimulus preference*

Results of a *t* test for independent samples indicated that there were no differences between UChA and UChB rats in the amount of time spent on the nonpreferred side before stimulus introduction [t ($n = 30$) = 3.5, $P < .001$]. Fig. 1 shows the time spent by ethanol-naive rats of the UChA and UChB lines on the acetaldehyde-paired and saline-paired sides. Two-way analysis of variance (ANOVA) of these data indicated that there was a significant difference between the two lines in the effect of acetaldehyde on the side preference [line × treatment interaction: $F(1,29) = 17.9$, $P < .001$]. Analysis of each line separately indicated a significant effect of treatment in the UChB [$F(1,14) = 26.57$, $P < .001$] and in the UChA [$F(1,14) = 44.71$, $P < .001$] rats. Post hoc analysis with Newman–Keuls comparisons indicated that the acetaldehyde dose of 50 mg/kg produced clear place preference in the UChB rats, because these animals spent more time on the acetaldehyde-paired side than on the saline-paired side. In contrast, the same acetaldehyde dose produced a very strong place aversion in UChA rats, because they spent more time on the saline-paired side than on the acetaldehyde-paired side.

3.2. *Effect of one dose of acetaldehyde on voluntary ethanol consumption*

Fig. 2 shows the voluntary ethanol intake [with free choice of 10% (vol./vol.) ethanol solution and water] 15 days before (Pre) and 4 weeks after (Post) the intraperitoneal administration of a 50-mg/kg dose of acetaldehyde or saline in UChA and UChB rats. There was a significant difference between the lines in the effect of acetaldehyde on ethanol

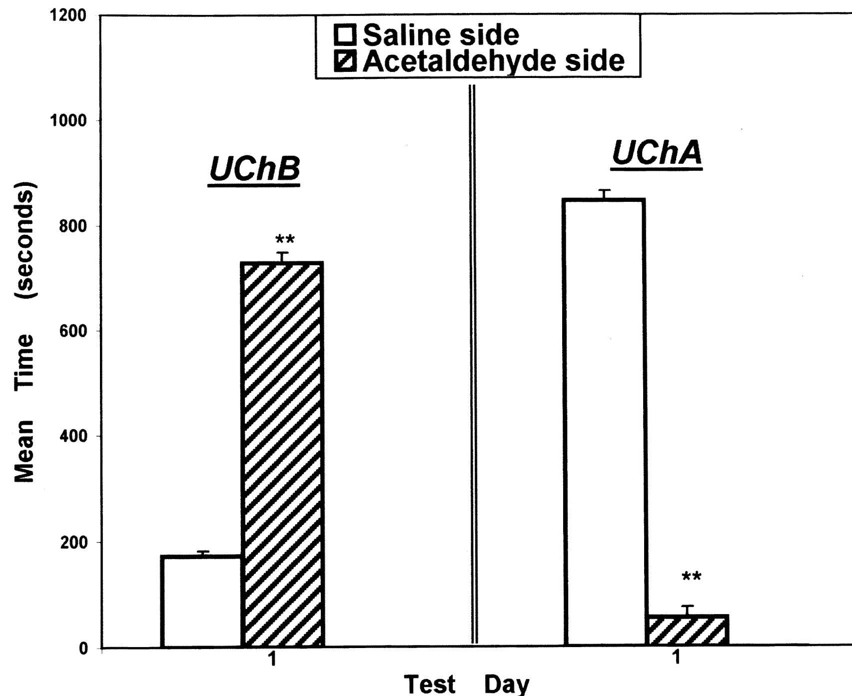

Fig. 1. Time spent on the sides of the test box paired with saline and with acetaldehyde (50 mg/kg, i.p.) for ethanol-naive high-alcohol-drinking (UChB) and low-alcohol-drinking (UChA) rats. Asterisks indicate significant differences between the time spent on the acetaldehyde side versus the saline side by the same rat line. $^{**}P < .001$.

consumption. This observation is supported by the results of a two-way ANOVA (line × treatment), which yielded significant effects of line [$F(1,160) = 224.9$, $P < .001$], treatment [$F(1,160) = 19.85$, $P < .001$], and line × treatment interaction [$F(1,160) = 50.3$, $P < .001$]. Separate analysis by one-way ANOVA of the voluntary ethanol consumption in UChB rats indicated a significant effect of acetaldehyde treatment [$F(3,79) = 24.4$, $P < .001$]. Post hoc analysis with Newman–Keuls comparisons indicated that after acetaldehyde treatment the ethanol consumption in UChB rats increased significantly with respect to the baseline amount exhibited before acetaldehyde treatment and with respect to the intake of the saline-treated UChB group. The increase in ethanol consumption appeared rapidly and remained for a long period, as it was elevated above the baseline when tested 4 weeks after the dose of acetaldehyde, as can be observed in Fig. 2.

With respect to UChA rats, a 50-mg/kg dose of acetaldehyde did not change their voluntary ethanol consumption, as the analysis indicated no significant effect of treatment [$F(3,79) = 1.28$, $P > .05$].

3.3. Cerebral blood acetaldehyde concentration

Table 1 shows the acetaldehyde concentration in cerebral venous blood samples, obtained from the superior sagittal blood sinus of UChA and UChB rats, at different times after an intraperitoneal injection of a 50-mg/kg dose of acetaldehyde. Cerebral venous blood acetaldehyde level was different between UChA and UChB rats [line × treatment interaction: $F(1,9) = 6.9$, $P < .001$]. Post hoc t test comparisons indicated that UChA rats, compared with UChB rats, displayed significantly higher blood acetaldehyde levels at all times after injection of a 50-mg/kg dose of acetaldehyde, indicating a slower rate of elimination of circulating acetaldehyde.

4. Discussion

In the current study, a pharmacologic intraperitoneal dose (50 mg/kg) of acetaldehyde, rather than a physiologic dose of acetaldehyde, was administered to the rats. Such a dose was used, so that it could be ascertained whether acetaldehyde crosses the blood–brain barrier.

Results from the current study indicate that rats, selectively bred for their high or low alcohol consumption, reacted differentially to this specific dose of acetaldehyde. UChB rats displayed preference, whereas UChA rats displayed aversion, for environmental cues previously paired with the acetaldehyde dose. These results indicate that acetaldehyde is primarily reinforcing to UChB rats and aversive to UChA rats. Although we used only one test dose of acetaldehyde, these results seem to indicate that the dose-dependent biphasic effects of acetaldehyde would be shifted to the left in

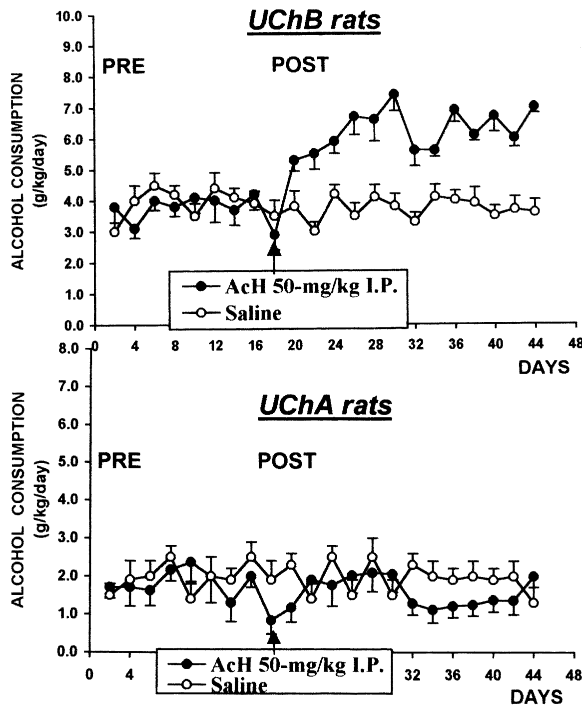

Fig. 2. Effect of one 50-mg/kg intraperitoneal dose of acetaldehyde (AcH) or saline on voluntary ethanol consumption in high-alcohol-drinking (UChB) (top panel) and low-alcohol-drinking (UChA) (bottom panel) rat lines. PRE = 15 days before and POST = 4 weeks after administration of acetaldehyde.

UChA rats, because they were more sensitive to the aversive effects. If the biphasic curve is shifted to the left, one could predict that a lower dose of acetaldehyde may induce place preference in UChA rats. This possibility could be examined in future studies. In addition, results showing that this acetaldehyde dose can increase the voluntary ethanol consumption in UChB rats, but not in UChA rats, support the suggestion that ethanol-derived acetaldehyde may act by regulating the ethanol consumption in both lines. The finding that, after administration of a 50-mg/kg dose of acetaldehyde, cerebral venous blood acetaldehyde levels in UChA rats were consistently higher than levels in UChB rats indicates a lower rate of acetaldehyde metabolism. The observed difference in blood acetaldehyde levels is presumably due to the previously reported line difference in the ALDH2 activity.

Table 1
Acetaldehyde concentration in cerebral blood samples obtained from low-alcohol-drinking (UChA) and high-alcohol-drinking (UChB) rats at different times after an acute intraperitoneal 50-mg/kg dose of acetaldehyde

	Blood acetaldehyde concentration (mg%)		
Rat line	2 min	5 min	10 min
UChA (n = 5)	3.12 ± 0.20	1.68 ± 0.28	0.36 ± 0.03
UChB (n = 5)	1.68 ± 0.09***	0.68 ± 0.08**	0.17 ± 0.02*

Values are means ± S.E.M.

Significant differences between UChA and UChB rats: $***P < .001$; $**P < .005$; $*P < .025$.

Results of studies in rat lines bred in Finland (Eriksson, 1968) for their voluntary low or high alcohol consumption [Alko Non-Alcohol (ANA) and Alko Alcohol (AA), respectively] have shown that ethanol administration results in higher blood acetaldehyde concentrations in the ethanol-avoiding ANA rat line (Eriksson, 1973), as a consequence of genetically lower ALDH activity, and this has been considered as the basis for the ethanol avoidance in this line (Koivisto & Eriksson, 1994). Such a view is in agreement with the hypothesis that the higher levels of acetaldehyde, obtained after the exogenous administration of acetaldehyde in UChA rats, were responsible for the aversive effects. However, the main ALDH isozyme responsible for this action in the ANA rats is different (microsomal) (Koivula et al., 1975) from the one in UChA rats (ALDH2). The UChA rat line seems to be a good model for the human *ALDH2*2* situation in the sense that these animals have a deficiency of the same isozyme (ALDH2) owing to a point mutation in the encoding gene (Sapag et al., 2003).

Because, in the majority of studies in which reinforcing properties have been attributed to acetaldehyde, the effects of acetaldehyde have been investigated by direct intracerebral infusion of acetaldehyde, peripheral accumulation of acetaldehyde has been associated with aversion, whereas its local accumulation within the brain has been associated with reinforcement (Brown et al., 1978). Nevertheless, results of a study in Wistar rats (Quertemont & De Witte, 2001) have shown that intraperitoneal injection of a 10- or 20-mg/kg dose of acetaldehyde was not only reinforcing; there also was no evidence of aversive effects with increasing doses of acetaldehyde (100 or 150 mg/kg). Such findings were interpreted as an indication that blood acetaldehyde accumulations are not always primarily aversive. Although UChB rats display lower blood acetaldehyde levels than those displayed by UChA rats, such blood acetaldehyde levels (Table 1) are virtually never obtained with ethanol intake, except after the pharmacologic inhibition of ALDH. Nevertheless, UChB rats did show place preference. These results, together with those of an earlier study in UChB rats (Quintanilla et al., 2002)—in which very high blood acetaldehyde levels, which were obtained with increasing doses of acetaldehyde (100 or 150 mg/kg, i.p.), did not induce aversion in these rats—are consistent with findings in Wistar rats (Quertemont & De Witte, 2002). Taken together, results of these studies support the suggestion that blood acetaldehyde concentration is not the primary factor determining the reinforcing or aversive effects of acetaldehyde in the rat.

The finding of a direct relation between brain ALDH activity and voluntary alcohol consumption in three strains of rats (Socaransky et al., 1984) supports the suggestion that it is the brain acetaldehyde metabolism, rather than its accumulation, that is the critical factor for mediating alcohol consumption. Results of an earlier study in UChA

rats, in which acetaldehyde levels in peripheral blood (determined in blood samples taken from the tip of the tail) after ethanol administration were very low and did not differ from acetaldehyde blood levels in UChB rats (Tampier et al., 1996), seem to indicate that brain acetaldehyde levels may be important in determining aversion or preference for alcohol. Therefore, we propose that, in the rat, a genetically or pharmacologically deficient activity of ALDH2 may lead to accumulation of acetaldehyde in the brain, which produces dysphoric effects and rejection of ethanol. It is not known how acetaldehyde produces dysphoric effects, but it has been postulated that it could cause perturbation of the normal brain function by inhibiting the ion-transferring ATPases (Na^{+}-, K^{+}-, and Mg^{2+}-activated) in cellular membranes (Tabakoff et al., 1976). On the other hand, a high brain ALDH level might reduce the level of ethanol-derived acetaldehyde, allowing UChB rats to drink larger amounts of ethanol before they experience the dysphoric effects.

Results of the current study also show a persistent and long-lasting enhancement of ethanol intake in UChB rats after one intraperitoneal dose (50 mg/kg) of acetaldehyde. Because this effect was observed when blood acetaldehyde levels diminished to zero, it is conceivable that the acetaldehyde oxidation could have induced the formation of one (or more) of the tetrahydroisoquinoline (TIQ) alkaloids in the brain of UChB rats. One of them, tetrahydropapaveroline (THP), is formed by condensation between dopamine and its own aldehyde 3-4-hidroxy-phenylacetaldehyde. Acetaldehyde may induce this condensation reaction through the competitive inhibition of the biogenic aldehyde oxidation by the ALDH (Davis & Walsh, 1970). The most striking effect of this alkaloid, in terms of alcohol, is related to the influence these compounds have on preference for alcohol. The direct introduction of a minute amount of THP (0.1–1 μg) in the lateral ventricle greatly increased voluntary alcohol consumption for many months (up to 10 months) in the rat (Myers, 1978; Myers & Melchior, 1977). In numerous studies, attempts have been made to identify sites of action in brain that are sensitive to the dopamine–aldehyde condensation products. Duncan and Fernando (1991) reported that a single injection of 1 μg of THP, placed in the region of a rat's brain that corresponds to the mesocorticolimbic system, increases the rat's preference for ethanol. Moreover, it has been reported that TIQs are inhibitors of dopamine uptake in nerve terminal (Heikkila et al., 1971), and that they also inhibit the enzymatic degradation of dopamine by blocking monoamine-oxidase and catecol-o-methyltransferase activities (Giovine et al., 1976). These actions would increase dopamine levels in brain regions associated with drug abuse (i.e., nucleus accumbens) (Koob, 1992).

In summary, the genetic mechanism apparently underlying the etiology of alcoholism could, in part, be expressed in terms of specific metabolic characteristics in the CNS. That UChA and UChB rat lines reacted differentially to a specific dose of acetaldehyde may be related to the variation in the voluntary selection of alcohol. On the basis of the findings obtained in the current study, an enhancement in alcohol drinking would more likely be associated with an increased brain acetaldehyde metabolism, through ALDH2, which might reduce the level of ethanol-derived acetaldehyde and might induce the formation of addictive-like metabolites such as THP by inhibiting competitively the biogenic aldehyde metabolism. In contrast, a low level of alcohol consumption would be associated more with a decreased brain acetaldehyde metabolism, which might result in accumulation of ethanol-derived acetaldehyde and dysphoric effects.

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