Pergamon

Pharmacology Biochemistry and Behavior, Vol. 52, No. 1, pp. 29-34, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00097-6

Effect of Ethanol on Extracellular Dopamine in the Nucleus Accumbens of Alcohol-Preferring AA and Alcohol-Avoiding ANA Rats

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Received 19 September 1994; Accepted 7 February 1995

KIIANMAA, K., M. NURMI, I. NYKÄNEN AND J. D. SINCLAIR. *Effect of ethanol on extracellular dopamine in the nucleus accumbens of alcohol-preferring AA and alcohol-avoiding ANA rats.* PHARMACOL BIOCHEM BEHAV 52(1) 29-34, 1995.—The role of central monoamines in the genetically determined influences on voluntary ethanol consumption were examined by studying the extracellular levels of monoamines in the nucleus accumbens of the alcohol-preferring AA (Alko Alcohol) and alcohol-avoiding ANA (Alko Nonalcohol) rats with in vivo microdialysis. Dialysate samples for the assay of monoamines with small bore HPLC were collected from freely moving animals at 15 min intervals after administration of ethanol (0.5, 1, or 2 g/kg, IP). Ethanol significantly increased the extracellular levels of dopamine, DOPAC, and HVA, suggesting stimulation of dopamine release by ethanol, while the effect on 5-HIAA did not reach significance. No difference in the extent or time course of stimulation of dopamine release between the AA and ANA rats was found. The results could so far give no indication that the differential ethanol consumption by AA and ANA rats could be explained in terms of differences in ethanol-induced stimulation of dopamine release in the nucleus accumbens.

Microdialysis Ethanol Selected lines Dopamine Nucleus accumbens

SELECTED lines can be a useful tool in studies on the mechanisms of ethanol consumption because the lines should theoretically differ from each other only in the trait upon which selection has been applied and in traits that are related to the selected trait (16). The AA (Alko Alcohol) and ANA (Alko NonAlcohol) rat lines have been developed by selective outbreeding (6-8,16,32) for differences in voluntary ethanol consumption. These lines have been used in studies on the role of central monoaminergic mechanisms of voluntary ethanol consumption (17,32). Central monoamines have been implicated in the self-administration of ethanol primarily because ethanol has been shown to alter the activity of central monoaminergic neurons in general. Ethanol has been found to increase the rate of accumulation of 3,4-dihydroxyphenylalanine (DOPA) after inhibition of aromatic aminoacid decarboxylase (2,15), and the levels of dihydroxyphenylacetic acid (DOPAC) in various brain parts (9,17,19,20). Similarly, data from electrophysiological studies have shown that ethanol increases the firing rate of neurons in the substantia nigra (11,18). The data on the activity of serotonergic neurons are not, however, that consistent [cf. (22)]. More recent studies using in vivo microdialysis or voltammetry have shown that ethanol increases the extracellular concentrations of dopamine and 5-hydroxytryptamine (5-HT) in the striatum and nucleus accumbens of freely moving rats, suggesting enhanced release after ethanol (4,5,13,30,36-38); the effect of ethanol on noradrenaline output in the frontal cortex, however, seems to be biphasic (29).

In the present work, the effects of ethanol on different monoamine neurotransmitters in the brain of AA and ANA rats have been studied to determine whether the difference in ethanol consumption between these lines could be related to the functions of the central monoaminergic neurons. Because the lines differ in ethanol preference, one may hypothesize that the monoaminergic neuronal systems also differ in their sensitivity to ethanol. Earlier studies using several conventional techniques have shown that although there are differences in the basal levels of monoamines, the AA rats showing

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higher levels of noradrenaline and lower levels of dopamine in various brain parts, the lines do not differ in the effect of ethanol on the rates of synthesis and metabolism of the monoamines (15,17). In accordance with these findings, the alcohol-preferring HAD and alcohol-avoiding LAD rats have been found not to differ in the effect of ethanol on the extracellular levels of dopamine (38).

The purpose of the present article was to test this hypothesis by studying the effect of various doses of ethanol on the extracellular concentrations of dopamine, DOPAC, homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) in the nucleus accumbens of freely moving AA and ANA rats using in vivo microdialysis, which allows monitoring extracellular concentrations of neurotransmitter substances in awake animals. The nucleus accumbens is innervated by the mesolimbic dopaminergic pathway, which has been hypothesized to play a role in the reinforcement by ethanol and other abused drugs [cf. (35)], and is, therefore, an obvious target for the studies.

METHOD

Animals

Naive male AA and ANA rats of the generations F64-66 and ranging from 3 to 4 months of age were used. They were housed in group cages, four to five rats of each line per cage, in a colony room with a 12L : 12D cycle, a temperature of approximately 22°C, and a relative humidity of 55%. Food (R3 Rat Feed, Evos Ab, Södertälje, Sweden) and water were freely available.

Approximately 10 days prior to surgery the rats were transferred from group cages in the colony rooms to single home cages of Plexiglas (24 × 24 × 30 cm), in a separate experimental room with conditions as above.

Surgery

The implantation of the guide cannula was made under halothane anesthesia: 3.5% for 4 min 30 s, then 1–2.5% as required when the rat was attached to the stereotactic frame. The guide cannula was lowered to a position just above the nucleus accumbens, 1.5 mm lateral to the midline, 1.7 mm anterior to the bregma, and 6.8 mm below the dura according to the atlas of Paxinos and Watson (24). The incisor bar was set at −3.3 mm. The cannula was fastened with dental cement anchored with three stainless steel screws to the skull. The rats were administered buprenorphine (Temgesic 0.3 mg/ml) 0.15 mg/kg SC immediately after surgery and during the next days if swelling was apparent and/or normal behavior was impaired. They were allowed to recover from surgery for at least 4 days. The rats were then accustomed to the microdialysis experimental situation. They were tethered to the counterbalancing arm for a few hours and picked up and restrained in the position used for injection on at least 3 days before the actual experiment took place.

Microdialysis

The experiments were started at 0900 h on each day by tethering the rat and inserting a CMA/11 probe (o.d. 0.24 mm, length 2 mm, polycarbonate membrane with a 20,000 Daltons cutoff) into the guide cannula. The flow rate from a CMA 100 microinjection pump (CMA/Microdialysis, Stockholm, Sweden), equipped with a 1 ml Hamilton syringe injecting modified Ringer solution (148 mM NaCl, 2.7 mM KCl, 1.2 mM CaCl, 0.85 mM MgCl), was set at 1.5 μl/min. The 15-min fractions were collected in vials containing 3 μl 1 mM glutathione in 0.05 M hydrochloric acid. The rats were injected with 0.5, 1.0, or 2.0 g/kg IP of ethanol (12% w/v) in saline (0.9% NaCl) 3 h after the probe had been inserted. The controls received an equal volume of saline. Dialysate samples were collected for 2 h after the injection.

The concentrations of monoamines in the dialysate samples were analyzed with high-performance liquid chromatography using electrochemical detection. The chromatograph system consisted of an ISCO Model 260D pump (Isco Inc., Lincoln, NB), a refrigerated autoinjector CMA/200, and an amperometric detector BAS LC-4B (Bioanalytical Systems Inc., West Lafayette, IN) with a glassy carbon working electrode. The sample components were separated with a small bore 3-μm ODS column (100 × 1.0 mm; Sepstik, BAS) using a 0.11 M phosphate buffer, pH 4.2, containing 0.22 mM octyl sodium sulphate, 0.13 mM EDTA, and 13% methanol. The flow rate of the mobile phase was 30 μl/min. The applied potential was 0.7 V. The chromatograms were recorded and processed using the Waters 820 Maxima Software (version 3.31). The retention times for DOPAC, dopamine, 5-HIAA, and HVA were 6.0, 7.5, 11.5, and 13.5 min, respectively.

Blood Ethanol Determination

For determination of the blood ethanol concentration, blood samples of 50 μl were drawn from the tip of the tail with a 50 μl capillary 30 min after the ethanol injection. The samples were blown into 450 μl distilled water in 22 ml GC vials. They were analyzed with headspace gas chromatography (Perkin-Elmer HS 100, GC Sigma 2000, Norwalk, CT) as described elsewhere (21).

Histology

After completion of the experiment, the position of the probe was verified by fixing the brain in formalin and then making frozen 100 μm coronal sections stained with thionine.

Data Analysis

The data are expressed as the percentage of the preinjection baseline values (i.e., the mean of four samples immediately preceding the injection). Differences between the groups were studied using analysis of variance followed by Student–Newman–Keuls test.

TABLE 1

THE BASAL EXTRACELLULAR LEVELS OF DOPAMINE, DOPAC, HVA, AND 5-HIAA IN THE NUCLEUS ACCUMBENS OF ALCOHOL-PREFERRING AA AND ALCOHOL-AVOIDING ANA RATS

Compound	AA	ANA
Dopamine	36.6 ± 5.7	37.5 ± 5.3
DOPAC	3.85 ± .36	3.99 ± .58
HVA	2.16 ± .20	2.23 ± .20
5-HIAA	2.93 ± .28	2.23 ± .22

The values (mean ± SEM) for dopamine are given in fmol/15 min, and for DOPAC, HVA, and 5-HIAA in pmol/15 min, n = 44–57.

RESULTS

There were no differences in the basal extracellular levels of dopamine, DOPAC, HVA, or 5-HIAA between the AA and ANA rats (Table 1).

Ethanol significantly increased the extracellular concentrations of dopamine (Fig. 1) in the nucleus accumbens of AA and ANA rats combined: $F(3, 81) = 2.87$, $p < 0.05$, for treatment, and, $F(7, 567) = 12.50$, $p < 0.001$, for time. The effect of ethanol seemed to be dose dependent: the effect was maximal in the dialysate samples collected 30 and 45 min after the administration of ethanol. There was no significant difference between the lines in the effect of ethanol over the entire 2-h period. Because possible line differences at the times of maximal ethanol effect (30 and 45 min) might have been obscured by inclusion of earlier and later times in the analysis, separate analyses of variance were conducted for just these peak times. Nevertheless, the line-by-dose interaction term was not significant at either 30 or 45 min after ethanol.

In parallel with its effect on dopamine, ethanol also significantly increased the extracellular concentrations of DOPAC in both lines combined: $F(3, 105) = 5.34$, $p < 0.01$, for ethanol, and, $F(7, 735) = 81.54$, $p < 0.001$, for time. The lines did not differ in the effect of ethanol on DOPAC concentrations, either (Fig. 2).

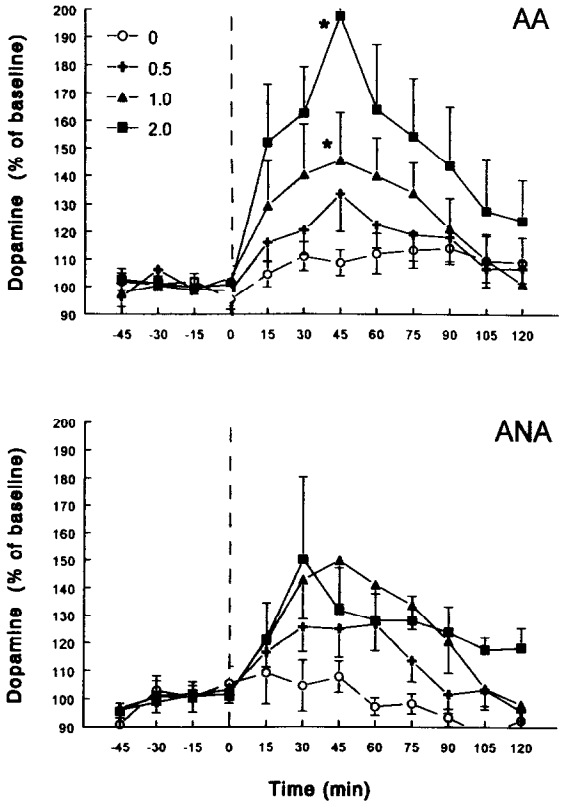

FIG. 1. The effect of an intraperitoneal injection of ethanol (0.5, 1.0, or 2.0 g/kg) on the extracellular levels of dopamine in the nucleus accumbens of alcohol-preferring AA and alcohol-avoiding ANA rats. The controls were injected with saline. The values are expressed as a percentage of the preinjection baseline levels. The dashed line indicates the time of injection. Means ± SEM of 6–17 animals are given. *$p < 0.05$ with respect to saline-injected control, Student-Newman-Keuls test.

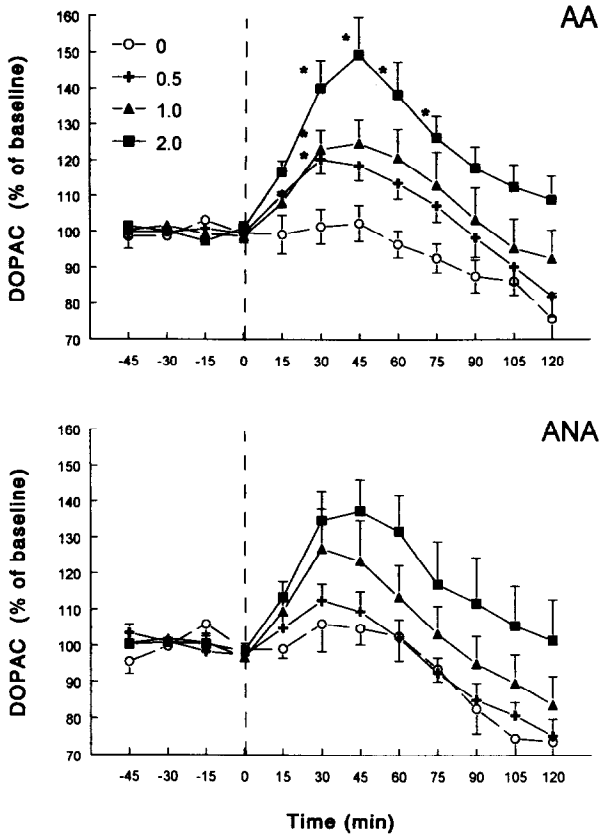

FIG. 2. The effect of an intraperitoneal injection of ethanol (0.5, 1.0, or 2.0 g/kg) on the extracellular levels of DOPAC in the nucleus accumbens of alcohol-preferring AA and alcohol-avoiding ANA rats. The controls were injected with saline. The values are expressed as a percentage of the preinjection baseline levels. The dashed line indicates the time of injection. Means ± SEM of 7–18 animals are given. *$p < 0.05$ with respect to saline-injected control, Student-Newman-Keuls test.

The extracellular concentrations of HVA (Fig. 3) were also significantly elevated in the two lines combined after ethanol: $F(3, 96) = 3.64$, $p < 0.05$, for ethanol, and, $F(7, 672) = 44.82$, $p < 0.001$, for time.

Ethanol also tended to enhance the extracellular concentrations of 5-HIAA, but the increase did not reach significance (Fig. 4).

The concentration of ethanol in the tail blood 30 min after administration of 0.5, 1, or 2 g/kg of ethanol IP is given in Table 2. The levels reached in the blood were not significantly different in the two lines. There seems to be a tendency for the ANA animals to show higher levels. This probably can be explained, however, by the fact that the ANA rats tend to be heavier, with generally more fatty tissue, than the AA rats (32), and, consequently, to develop slightly higher blood ethanol levels from the same g/kg dose of ethanol. There is, however, no indication that this would have affected the extracellular dopamine levels, because these tended to be lower in the ANA rats.

DISCUSSION

The present experiments showed that intraperitoneal administration of ethanol in doses of 0.5–2 g/kg increased the

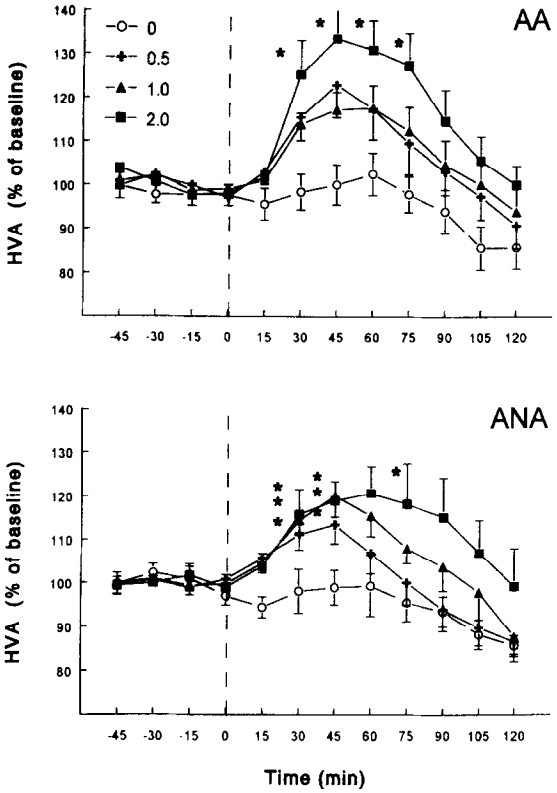

FIG. 3. The effect of an intraperitoneal injection of ethanol (0.5, 1.0, or 2.0 g/kg) on the extracellular levels of HVA in the nucleus accumbens of alcohol-preferring AA and alcohol-avoiding ANA rats. The controls were injected with saline. The values are expressed as a percentage of the preinjection baseline levels. The dashed line indicates the time of injection. Means ± SEM of 7–16 animals are given. *$p < 0.05$ with respect to saline-injected control, Student-Newman-Keuls test.

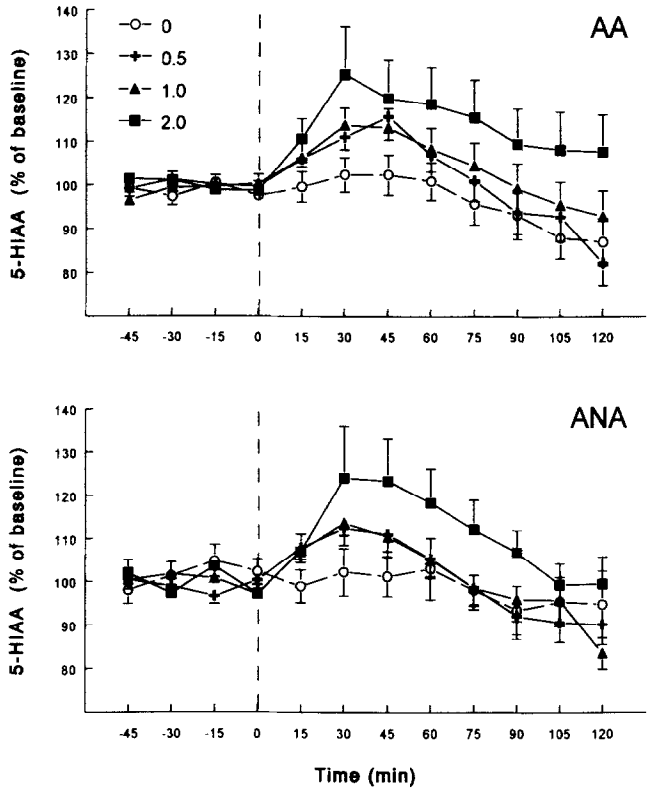

FIG. 4. The effect of an intraperitoneal injection of ethanol (0.5, 1.0, or 2.0 g/kg) on the extracellular levels of 5-HIAA in the nucleus accumbens of alcohol-preferring AA and alcohol-avoiding ANA rats. The controls were injected with saline. The values are expressed as a percentage of the preinjection baseline levels. The dashed line indicates the time of injection. Means ± SEM of 6–18 animals are given. *$p < 0.05$ with respect to saline-injected control, Student-Newman-Keuls test.

extracellular levels of dopamine in the nucleus accumbens of alcohol-preferring AA and alcohol-avoiding ANA rats. These data are in agreement with previous microdialysis studies showing that ethanol can augment the output of dopamine in the nucleus accumbens and suggesting an increase in dopamine release (13,30,34,37,38). Ethanol increased also the extracellular levels of DOPAC and HVA, in accord with some earlier studies [(13,30); but see (37,38)]. The increases in the extracellular levels of dopamine and its metabolites suggest an enhancement in the release and metabolism of dopamine in the nucleus accumbens after ethanol administration.

TABLE 2

THE CONCENTRATION OF ETHANOL IN THE TAIL BLOOD OF ALCOHOL-PREFERRING AA AND ALCOHOL-AVOIDING ANA RATS 30 MIN AFTER ADMINISTRATION OF ETHANOL 0.5, 1, OR 2 g/kg IP

Ethanol Dose	AA	ANA
0.5	6.23 ± 0.49	7.34 ± 0.43
1.0	17.8 ± 1.55	19.7 ± 1.02
2.0	40.0 ± 3.04	49.4 ± 2.53

The values (mean ± SEM) are given in mM; n = 14–19.

The extracellular levels of 5-HIAA were not significantly modified by ethanol. This finding is in agreement with the earlier work showing that ethanol can increase the levels of 5-HT but has no effect of the concentrations of 5-HIAA (26,37,38). Furthermore, it should be noted that the relationship between extracellular concentrations of 5-HIAA and serotonergic transmission is rather complex (14).

In contrast to our hypothesis precipitating this study, no significant difference was found between the AA and ANA rat lines in the effect of ethanol on the extracellular levels of dopamine or its metabolites. On the basis of this study alone, we cannot, of course, accept the null hypothesis that no difference exists between the lines on these variables. Nevertheless, the study was sufficiently large and powerful to allow the conclusion that if there is a line difference here, it is not an important contributor to the variation. Furthermore, close examination of the data shows that although there is a large amount of interindividual variation within each line, the results from a single animal are relatively constant over time with, e.g., peaks being preceded and followed by elevated values rather than standing alone. Therefore, the variability

appears not to arise from methodological problems. We suspect that the variability seen in these effects of ethanol are, instead, caused mainly by large individual differences in the levels of ethanol in the brain, particularly early after administration, as was seen in our previous work (21). The lack of a significant line difference suggests further that these differences either are beyond genetic control or are unimportant for alcohol drinking.

This lack of line difference is in accord with our earlier postmortem analysis studies demonstrating that ethanol increased the levels of DOPAC and HVA in the different brain parts of AA and ANA rats in a similar manner (15,17). Interestingly, this is also fully in accord with the studies showing that there is no difference in the effect of ethanol (0.5–2 g/kg IP) on the extracellular levels of dopamine in the nucleus accumbens between two other selectively bred rat lines, high-alcohol-drinking HAD and low-alcohol-drinking LAD rats (38).

Some studies have, however, found a relationship between predisposition to ethanol intake and the magnitude of the effect of ethanol on dopaminergic neurons. For instance, the effect of ethanol (1.25 g/kg IP) on the metabolism of dopamine in the nucleus accumbens was more marked in the high-drinking individuals from an unselected stock of Wistar rats than in the nonpreferring individuals, when monitored with in vivo voltammetry (5), suggesting that alcohol-preferring animals show more dopamine release after ethanol than alcohol-nonpreferring animals. In line with these results, the levels of DOPAC and HVA in postmortem tissue samples from caudate nucleus, olfactory tubercle, and medial prefrontal cortex after an intragastric load of 2 g/kg of ethanol were higher in the ethanol-preferring sP rats than in those of the ethanol-nonpreferring sNP rats (10). Furthermore, a strain difference in the magnitude of the effect of self-administered ethanol on dopamine overflow in the nucleus accumbens was found between alcohol-preferring P rats and genetically heterogenous Wistar rats in a free-choice operant task (33,34), giving further support to the idea that ethanol-induced increase in the extracellular levels of dopamine may in some circumstances depend upon the predisposition to self-administer ethanol.

There obviously is a discrepancy between the studies finding no difference in the effect of ethanol on dopaminergic transmission, in vivo or postmortem, among rat lines selected for differential ethanol intake (15,17,38), and the postmortem (9) and in vivo (5,33,34) studies finding a relationship between the effect of ethanol on dopaminergic neurons and predisposition to ethanol consumption. There are, however, clear differences between the studies, which may be important in terms of our hypothesis, and may help to explain the differential results. First, only in the present study and in the one by Yoshimoto et al. (38) were the effects of ethanol on dopamine efflux examined with microdialysis in the nucleus accumbens of rat lines selected for differential ethanol intake, which makes the two studies comparable in terms of the method and material used. The results obtained were also consistent. In the other in vivo studies, the animals were not comparable in the same sense. The study by Engel et al. (5) was based on the use of unselected Wistars, while in the study by Weiss et al. (34) Wistar and P rats were compared. Neither of the latter approaches, however, gives the same benefits as the use of selected lines, for determining what traits are related to different predispostions to ethanol consumption (16). This is because selected lines are produced by selectively breeding animals from the same base population for a specific ethanol-related trait; the selected lines should theoretically differ from each other only in the trait upon which selection has been applied and in traits that are related to the selected trait either causally or through genetic linkage.

Another major and probably even more important difference between the studies using selected lines and the other two studies was that in the former ethanol-naive animals were used, while in the latter studies the rats had had prior access to ethanol solution. The prior access may have caused a sensitization of the dopaminergic reaction. An increase and the exposure to ethanol is suggested by both neurochemical (3) and behavioral (12) work. Furthermore, sensitization of dopaminergic neurons to the effects of other drugs of abuse, such as amphetamine and cocaine has sometimes been reported [(1, 23,25,27); but see (31)].

Sensitization might explain the discrepancies between the studies if alcohol-preferring individuals developed more sensitization than do alcohol-avoiding animals after the same amount of ethanol experience. Related to this idea, it has been speculated that an increase in sensitivity may be a factor that contributes to the development of preference and addiction to ethanol and other abused drugs (28).

A simpler explanation, at least in the case of the Engel et al. (5) study, is that the alcohol-preferring rats had a larger dopaminergic response to ethanol because they had consumed more ethanol during the prior weeks of exposure: their greater intake then caused more sensitization. The Weiss et al. (34) study, however, favors the former explanation because it examined Wistar and P rats that had apparently had similar amounts of prior alcohol experience.

Whether either differential sensitization susceptibility or differential exposure can explain the discrepancies, on one hand, between the present results and our instigating hypothesis, and on the other hand, between the different studies, remains to be determined. In particular, more needs to be known about the effect of repeated ethanol treatment on the responsiveness of dopaminergic neurons to ethanol in the AA/ANA and other selected rat lines.

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