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Effect of prior ethanol experience on dopamine overflow in accumbens of AA and ANA rats

Maria Nurmi [b], Takeshi Ashizawa [a,1], J. David Sinclair [a], Kalervo Kiianmaa [a,*]

[a] *Department of Alcohol Research, National Public Health Institute, POB 719, FIN-00101 Helsinki, Finland*
[b] *Department of Ecology and Systematics, Zoological Laboratory, University of Helsinki, FIN-00014 Helsinki, Finland*

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Abstract

The purpose of this study was to investigate the effect of repeated ethanol administration on dopamine overflow in the nucleus accumbens of alcohol-preferring AA (Alko Alcohol) and alcohol-avoiding ANA (Alko Nonalcohol) rats. Dopamine is a possible mediator of the reinforcing effects of ethanol, but it has previously been shown that ethanol-naïve alcohol-preferring AA and alcohol-nonpreferring ANA rats do not differ in their dopaminergic reaction to an intraperitoneal ethanol injection (0.5–2.0 g/kg), as assessed by measuring extracellular dopamine in the nucleus accumbens with in vivo microdialysis. Here a group of AA rats drank 10% (v/v) ethanol voluntarily – continual access for 5–15 days, limited access for 3 weeks – while a yoked group of AA rats and a yoked group of ANA rats received the same amount intragastrically by intubation. The rats were implanted with guide cannulas on the fourth week of limited access. Dopamine overflow was monitored in the microdialysis perfusate after 1 g/kg i.p. ethanol. The AA and the ANA rats that received ethanol non-contingently showed the same dopaminergic response to this as naïve animals have before. The group that had ingested the ethanol voluntarily showed, however, a significantly smaller increase in dopamine after 1 g/kg ethanol i.p. This suggests that the active behavior associated with obtaining the contingent drug may have an important impact on the reactions of the dopamine system to the drug, producing different results than when the same drug is admistered by other routes. The hypothesis that dopamine mediates ethanol reinforcement in AA rats is not supported by the results.

Keywords: Nucleus accumbens ; Dopamine ; Ethanol ; Microdialysis ; Tolerance ; Animal model

1. Introduction

Dopamine has been thought to play an important role in reinforcement, craving and incentive motivation with various drugs of abuse, including ethanol (Wise and Bozarth, 1987; Koob and Bloom, 1988; Robinson and Berridge, 1993; Di Chiara, 1995). There also has been speculation that genetic differences in the dopamine system are related to the risk of developing alcoholism, but the results are inconsistent (Blum et al., 1990, 1991; Uhl et al., 1993; but see Bolos et al., 1990; Goldman et al., 1993).

The mesolimbic dopaminergic system, which has been linked to theories of drug reward, has been shown in microdialysis studies on rats to be affected by several drugs of abuse (Di Chiara and Imperato, 1988; Pettit and Justice, 1991; Camp et al., 1994; Hemby et al., 1995). Similar to these other drugs, but with a lower percentual increase, ethanol increases the extracellular concentration of dopamine in the striatum and nucleus accumbens of rats (Imperato and Di Chiara, 1986; Yoshimoto et al., 1991; Weiss et al., 1993; Kiianmaa et al., 1995).

Because of the purported involvement of dopamine in alcohol drinking, the central monoaminergic mechanisms of the alcohol-preferring AA (Alko Alcohol) and the alcohol-avoiding ANA (Alko Non Alcohol) rats, developed for differential ethanol intake in a free choice situation (Eriksson, 1968, 1969; Eriksson and Rusi, 1981; Kiianmaa et al., 1992), have earlier been studied with conventional techniques (Kiianmaa and Tabakoff, 1984; Sinclair et al., 1989; Kiianmaa et al., 1991). Although line differences in basal monoamine levels were found, with higher levels of noradrenaline and lower levels of dopamine in various parts of the brain in AA rats, no differences were found in the rate of synthesis or metabolism of the monoamines.

* Corresponding author. Tel.: (358-9) 133-2826; Fax: (358-9) 133-2781; e-mail: kalervo.kiianmaa@ktl.fi

[1] Present address: Department of Neuropsychiatry, Sapporo Medical College, Sapporo, Japan.

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Microdialysis studies have shown a dose-dependent increase in the concentration of extracellular dopamine in the nucleus accumbens of both the AA and the ANA rats after intraperitoneal ethanol doses of 0.5, 1.0 and 2.0 g/kg (Kiianmaa et al., 1995). No difference between the rat lines was found, however, in the amount or temporal pattern of ethanol-induced stimulation of dopamine release, which might suggest that the reinforcement from ethanol is not related to the amount of dopamine released by ethanol.

These previous microdialysis studies, however, used ethanol-naïve animals, whereas the line difference in ethanol preference is not seen in animals without prior ethanol experience; instead it is established during the weeks when the rats have a free choice between ethanol and water. Consequently, the present work was designed to study the dopaminergic response in the nucleus accumbens of AA and ANA rats that have had experience with ethanol.

We included three different groups: AA rats that drank ethanol voluntarily and AA and ANA rats that were intragastrically (i.g.) intubated with yoked amounts (g/kg) of ethanol. Since the ANA rats drink almost no ethanol voluntarily, they are only represented by the group that received ethanol passively. After a prolonged period of limited ethanol access and yoked intragastric ethanol administration the rats took part in a microdialysis experiment where they were given an intraperitoneal (i.p.) ethanol injection (1 g/kg), and the changes in extracellular dopamine, DOPAC (dihydroxyphenylacetic acid) and HVA (homovanillic acid) were monitored in the perfusate.

2. Materials and methods

2.1. Repeated ethanol administration

Three groups of male rats, matched for initial body weight, were used in the experiment: group AA-drink composed of AA rats that voluntarily drank 10% (v/v) ethanol (see details below); group AA-intragastric composed of AA rats that were intubated intragastrically to receive 10% ethanol; and group ANA-intragastric composed of ANA rats also intubated to receive 10% ethanol. The mean body weight of all rats at the beginning of ethanol administration was 393 ± 6 g (mean $\pm$ S.E.M.), ranging from 317 to 487 g, $n = 47$, with no significant weight differences between the groups.

The rats were placed in single plexiglas cages ($24 \times 24 \times 30$ cm) located in an experiment room where they were kept throughout the different stages of the procedure: i.e., the preadministration of ethanol and the microdialysis study. The room temperature was kept at 20 ± 1°C, the relative humidity at 50 ± 5%, and a 12-h light/dark cycle with lights on at 06:00 was used. The rats had access to normal maintenance food (RM1 (E) SQC pellets from SDS, Witham, UK) and tap water at all times.

The rats in group AA-drink were given ethanol to drink according to a modified limited access paradigm (Sinclair et al., 1992). At first, they were offered a two-bottle choice between ethanol (10%, v/v) and water continuously. The AA-intragastric and ANA-intragastric groups received three times daily (at 8 a.m., 1 p.m. and 5 p.m.) the amount of ethanol in g/kg that their matched pair in the AA-drink group had consumed during the previous 24 h. The maximal volume administered by intubation at one time was 5 ml. If the dose required a larger volume, additional intubations were made at 30-min intervals to avoid distention of the stomach.

The rats had 5–15 days of continual ethanol access. The mean ethanol intake during the last 5 days was 4.11 ± 0.20 g/kg/day, ranging from 0.5 to 7.8 g/kg/day. The rats were then switched to 30 min/day access to 10% ethanol, beginning at 13:00. After the daily ethanol access for the AA-drink rats, their yoked pairs in the other two groups received the amount they had drunk. The average intake during the 30-min access to ethanol was 0.49 ± 0.02 g/kg (range 0–1.57 g/kg). This stage lasted 3 weeks; during the 4th week the rats were implanted with a guide cannula for microdialysis. The rats were given ethanol every day except on the day of surgery and the day after. Thus there was no prolonged period of ethanol deprivation before the experiment. The mean total amount of ethanol consumed before the microdialysis experiment was 54 ± 7 g/kg per rat.

2.2. Surgery

The rats were implanted with a guide cannula under halothane anesthesia (3.5% for 4.5 min, then 1.5–2.5% during surgery) in a stereotactic frame. The guide cannula was aimed at a point above the nucleus accumbens at 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 (1982). The incisor bar was set at -3.3 mm. Three stainless steel screws were fastened to the skull to stabilize the dental cement which was used to hold the cannula in place.

The rats were administered 0.15 mg/kg buprenorphine (Temgesic, 0.3 mg/ml) subcutaneously immediately after the surgery. Further injections during the next days were given if normal behavior was impaired or swelling was apparent. The rats were put back on the limited access schedule or the yoked intubations when pain killer was no longer needed, which was usually the day after surgery. There were 7 days between surgery and microdialysis experiment.

The rats were trained in the microdialysis setup before the experiment day: i.e., they were attached to the counterbalancing arm in their home cage, until they were indifferent to the apparatus.

2.3. Microdialysis routine

The yoked animals were always treated on the same day. Thus, there were three microdialysis experiments in parallel. The probes, CMA/11 (2 mm long, o.d. 0.24 mm, CMA/Microdialysis, Stockholm, Sweden), were inserted at 8:00 and the flow rate of the modified Ringer solution (148 mM NaCl, 2.7 mM KCl, 1.2 mM $CaCl_2$, 0.85 mM $MgCl_2$) from a CMA 100 microinjection pump was set at 1.5 μl/min. The tip of the tail was cut for blood samples to be taken after ethanol administration. The perfusion was continued and 10 min fractions were collected. The rats were given a saline (0.9% NaCl) injection 3.5 h after probe insertion, and then 6 baseline perfusate samples were collected. One hour after the saline injection an i.p. ethanol injection of 1 g/kg (as 10% (w/v) in saline) was administered, and samples were collected every 10 min for 2 h. At 60 min after ethanol administration, 20 μl blood samples were drawn from the tail and analyzed by headspace gas chromatography, as described elsewhere (Nurmi et al., 1994).

2.4. HPLC

The 15-μl samples were collected into microvials containing 3 μl 1 mM glutathione in 0.05 mM HCl. They were immediately refrigerated and analyzed by high-performance liquid chromatography (HPLC) using electrochemical detection. The sample was injected with a refrigerated autoinjector CMA/200 into 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, set by an ISCO Model 260D pump (Isco, Lincoln, NB, USA), of the mobile phase was 30 μl/min. The monoamines were detected with an amperometric detector BAS LC-4B (Bioanalytical Systems, West Lafayette, IN, USA) with a glassy carbon working electrode. The applied potential was 700 mV. The chromatograms were recorded and processed with Waters 820 Maxima Software (version 3.31).

2.5. Histological verification

After the experiment, the brains of the rats were removed and fixed in formalin. 100-μm-thick coronal frozen slices were stained with thionine, and the position of the probe was verified.

2.6. Statistical methods

The raw data (pmol or fmol/10 min) were converted into percentages of the baseline consisting of the mean of the last three saline samples. An analysis of variance with repeated measures over time was used with Newman-Keuls test where appropriate. The data were also analyzed as differences in concentration, i.e. Δ (mol/10 min). The absolute concentration in each sample was subtracted from the absolute concentration of the mean of the three samples preceding the ethanol injection to balance for the interanimal variation in baseline dopamine. This did not change the overall picture, and the statistical tests made on these transformed data produced indentical results. The data are presented as percentage of baseline.

3. Results

The intraperitoneal injection of 1 g/kg ethanol increased the extracellular concentration of dopamine

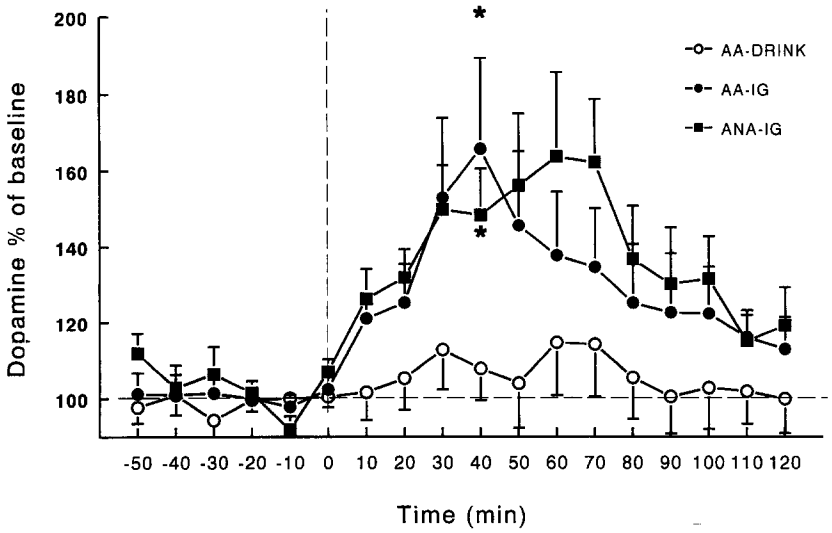

Fig. 1. The effect of repeated ethanol pre-administration on dopamine overflow in the nucleus accumbens after 1 g/kg i.p. (dashed vertical line), mean ± S.E.M. for 9–12 rats. The values are expressed as percentage of the baseline level. The AA-drink (AA-DRINK) group self-administered ethanol during the pre-administration period, while the yoked AA-intragastric (AA-IG) and ANA-intragastric (ANA-IG)groups were intubated to receive ethanol intragastrically. * $P < 0.5$ with respect to AA-drink, Student-Newman-Keuls test.

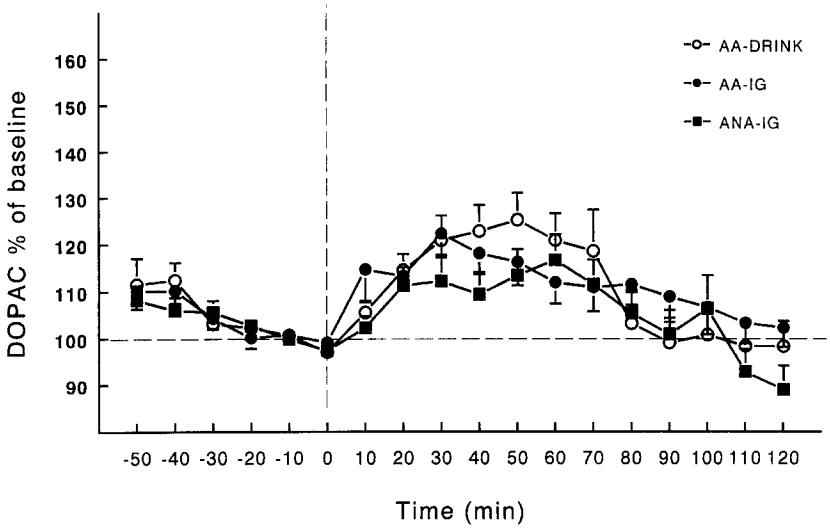

Fig. 2. The effect of repeated ethanol pre-administration on DOPAC overflow in the nucleus accumbens after 1 g/kg i.p. (dashed vertical line), mean ± S.E.M. for 10–16 rats. The values are expressed as percentage of the baseline level. The AA-drink (AA-DRINK) group self-administered ethanol during the pre-administration period, while the yoked AA-intragastric (AA-IG) and ANA-intragastric (ANA-IG) groups were to receive ethanol intragastrically.

($F(5,30) = 4.04$, $P < 0.0018$). The dopamine levels during the first hour after ethanol were, however, significantly lower in the group of AA rats that had voluntarily drunk ethanol during the pre-administration period than in the AA and ANA groups that received the ethanol passively by intragastric administration ($F(2,30) = 3.66$, $P = 0.0377$ during the 1st h after ethanol, $n = 9–12$, see Fig. 1). The AA-intragastric and ANA-intragastric groups both had peak dopamine concentrations that were approximately 60% above baseline, but the AA-drink group showed less than a 20% increase in dopamine. This increase was not significant.

Ethanol also increased DOPAC ($F(5,37) = 7.29$, $P < 0.0001$, $n = 10–16$, Fig. 2) and HVA ($F(5,33) = 9.02$, $P < 0.0001$, $n = 12–13$, Fig. 3) in all three groups, but there were no significant differences between groups.

The mean ± S.E.M. baseline concentration of dopamine was for the AA-drink, AA-intragastric and ANA-intragastric groups 14.8 ± 2.1 fmol/10 min, 11.2 ± 2.3 fmol/10 min and 11.0 ± 1.8 fmol/10 min, respectively; for DOPAC 1.7 ± 0.4 pmol/10 min, 1.1 ± 0.2 pmol/10 min and 1.7 ± 0.4 pmol/10 min; and for HVA 1.0 ± 0.1 pmol/10 min, 0.9 ± 0.1 pmol/10 min and 1.0 ± 0.1 pmol/10 min. There were no significant differences be-

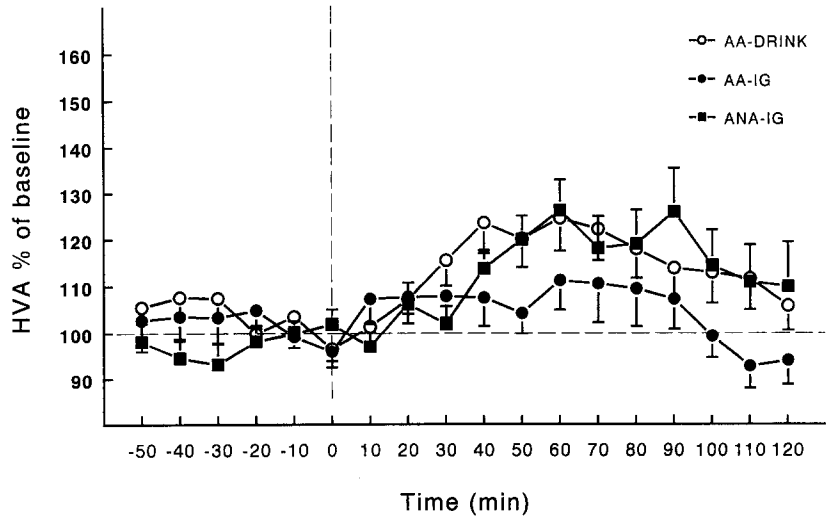

Fig. 3. The effect of repeated ethanol pre-administration on HVA overflow in the nucleus accumbens after 1 g/kg i.p. (dashed vertical line, mean ± S.E.M. of 12–13 rats.). The values are expressed as percentage of the baseline level. The AA-drink (AA-DRINK) group self-administered ethanol during the pre-administration period, while the yoked AA-intragastric (AA-IG) and ANA-intragastric (ANA-IG) groups were intubated to receive ethanol intragastrically.

tween the baseline values between the groups. Blood ethanol concentrations were: 17.2 ± 1.0 mM for the AA-drink group, 16.6 ± 1.1 mM for the AA-intragastric group and 19.3 ± 1.1 mM for the ANA-intragastric group, with no significant differences between the groups.

4. Discussion

An i.p. injection of 1 g/kg ethanol increased the dopamine concentration in the extracellular perfusate of the nucleus accumbens. The magnitude of this dopaminergic increase in the animals that had received ethanol only passively during pretreatment was similar to that found previously in ethanol-naïve AA and ANA rats (Kiianmaa et al., 1995). The magnitude was, however, markedly smaller in animals which had drunk the ethanol. Tolerance is defined as a reduction in the response elicited by a given dose of a drug. Therefore, the reduction in the dopaminergic response seen here is, by definition, an example of tolerance. It is a rather special measure of tolerance because it involves not an overt behavioral or physiological response but rather a response within the central nervous system. The dose of 1 g/kg is a modest ethanol dose by comparison and behavioral tolerance was not evaluated, since the signs of tolerance would be subtle and difficult to rate (compare Rossetti et al., 1993).

Interestingly, the development of tolerance to ethanol seen in the dopamine response was dependent upon the mode of ethanol administration: only the group that drank the ethanol showed this reduction in the dopamine response. The other two groups receiving the same amounts of ethanol daily by intubation continued to show large dopamine responses. Their failure to show tolerance is in agreement with the results of Rossetti et al. (1993), where tolerance to ethanol-induced dopamine release was not found in rats administered ethanol by the experimenter. Also, tolerance to experimenter-administered injections of nicotine was not found for dopamine release in the nucleus accumbens, although tolerance to the nicotine-induced locomotor depression was seen (Damsma et al., 1989). Hurd et al. (1989) found that contingent cocaine in animals with experience of self-administration did not elevate dopamine levels in the nucleus accumbens, whereas self-administered cocaine in drug-naïve animals elicited enhancement of dopamine overflow. In contrast, Meil et al. (1995) did not find this attenuation of dopamine after either contingent or non-contingent cocaine on the first day of withdrawal but the effect was apparent after 7 days of withdrawal.

The present results are contrary to what was expected on the basis of the hypothesis that dopamine mediates reinforcement of ethanol drinking (Wise and Bozarth, 1987; Di Chiara, 1995; but see Robinson and Berridge, 1993). First, behavioral studies have shown that ethanol is positively reinforcing for AA rats but not for ANA rats (Sinclair, 1974; Hyytiä and Sinclair, 1991), but no difference was seen between the dopamine responses to ethanol of the AA-intragastric and the ANA-intragastric groups.

Second, if the animals had all been given ethanol to drink at the time when the microdialysis test was done, the AA-drink group would probably have consumed more ethanol than the AA-intragastric group, as was seen in a similarly designed experiment with Long Evans rats (Sinclair et al., 1973). The fact that the AA-drink group showed no significant release of dopamine after ethanol and significantly less release than the AA-intragastric group is contrary to the hypothesis that ethanol-induced dopamine release reinforces and/or promotes ethanol drinking.

Third, along a similar line, tolerance has been found not to develop to the reinforcing effects of ethanol. This has been shown in rats with intravenous ethanol self-administration (Numan, 1981), in an operant drinking situation (Sinclair, 1974; Hyytiä and Sinclair, 1991), and in a place preference paradigm (Bozarth, 1990), and in mice with ethanol-induced locomotor activity (Tabakoff and Kiianmaa, 1982). Consequently the neurochemical factor mediating ethanol reinforcement probably does not show tolerance. In our study the AA rats which had made the active response of drinking ethanol showed a decreased output of dopamine in the nucleus accumbens after an acute 1 g/kg i.p. injection compared to the AA and ANA rats that had received ethanol passively during pretreatment. Therefore, the result does not support the hypothesis that dopamine is responsible for ethanol reinforcement in AA rats. We cannot exclude the possibility that dopamine might be important for the P line of alcohol-preferring rats, as has been suggested (Weiss et al., 1993).

The possibility also cannot be excluded without further research that the difference in tolerance development seen in the present study was caused by the temporal patterns of administration: the self-administering rats apparently received their ethanol more frequently but in smaller doses than the other rats which generally had only three doses of ethanol daily during the continual ethanol access. However, since the rats in the limited access situation normally start drinking immediately and consume most of the ethanol in a few drinking bouts within 5 min, the temporal changes in brain ethanol level are probably very similar to those after intragastric administration of the same dose of ethanol (Nurmi et al., 1994).

There are other reports of a differential reaction to drugs depending on the mode of administration. Hemby et al. (1995) found that experimenter-administered intravenous heroin caused an increase in extracellular dopamine in the nucleus accumbens whereas self-administered heroin did not. In contrast with the present experiment, however, they did not examine whether prior experience with contingent heroin caused tolerance to a non-contingent test dose. Heroin has also been shown to increase the extracellular dopamine concentration in the nucleus accumbens during intravenous self-administration in rats (Wise et al., 1995). Enhancement by ethanol of intracranial self-stimulation

has been reported to occur only with self-administered ethanol and not with externally determined intragastric ethanol administration (Moolten and Kornetsky, 1990), supposedly because the amount of control the animals have over drug administration is important for the rewarding effects. Honkanen et al. (1995) reported that i.p. ethanol did not induce locomotor stimulation in either AA or ANA rats, while an earlier study showed that voluntary ethanol drinking increases locomotor activity in the AA rats (Päivärinta and Korpi, 1993), thus pointing out a behavioral difference after contingent and non-contingent ethanol. The present result has perhaps the closest resemblance to the finding (Dworkin et al., 1992) that rats self-administering cocaine intravenously develop tolerance to the anorectic effect of the drug and have a lower rate of morbidity than do yoked control rats receiving the same dose non-contingently.

Repeated use of psychostimulatory drugs (such as cocaine and amphetamine) has been reported to cause an increase in the drug-induced release of dopamine in the striatum or nucleus accumbens (Robinson et al., 1988; Akimoto et al., 1989; Pettit et al., 1990; Patrick et al., 1991; Parsons and Justice, 1993; Banks and Gratton, 1995; Williams et al., 1995; but see Segal and Kuczenski, 1992a,b): i.e., to cause sensitization rather than tolerance in the dopamine response. This may not be inconsistent with the present findings because the same drugs normally show sensitization with respect to overt responses, while tolerance in overt responses is generally found with ethanol.

We have yet to find a completely satisfactory explanation for this drinking-dependent tolerance. One could, however, imagine that only contingent ethanol allows the brain to adapt in a manner counteracting the effects of ethanol on dopamine release, even if the subsequent ethanol itself is experimenter administered.

Alternatively, one could suppose that contingent ethanol causes initially a larger dopamine release and thus stimulates more development of tolerance than does a non-contingent dose. This is analogous to reinforcement contrast effects, e.g., one pellet of food is less valuable to a rat that has previously received two pellets than to a rat used to getting only one; thus non-contingent ethanol is less valuable (i.e. stimulates less dopamine release) in a rat with contingent ethanol experience than in rats used to non-contingent ethanol. Thus dopamine could be important for promoting initial ethanol drinking while the substance is still novel for the AA animals (Robinson and Berridge, 1993; Di Chiara, 1995).

We saw no difference in the DOPAC or the HVA increase between the groups that received ethanol contingently and non-contingently during pretreatment (compare Yoshimoto et al., 1991, 1992; Imperato and Di Chiara, 1986; Rossetti et al., 1993). Therefore, increases in dopamine metabolism might have been responsible for or contributed to the lower dopamine levels seen in the AA-drink group. However, the use of metabolite levels in assessing dopamine release is problematic, and both neuronal (Zetterström et al., 1988) and microdialysis factors (Yoshimoto et al., 1991) can affect the result.

In conclusion, although again no difference between AA and ANA rats was found in their ethanol-induced increase in extracellular dopamine, the response was greatly reduced by prior ethanol drinking but not by prior intragastric administration of ethanol in the same doses.

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