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BRIEF COMMUNICATION

Effects of Ventral Striatal 6-OHDA Lesions or Amphetamine Sensitization on Ethanol Consumption in the Rat

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FAHLKE, C., S. HANSEN, J. A. ENGEL AND E. HÅRD. *Effects of ventral striatal 6-OHDA lesions or amphetamine sensitization on ethanol consumption in the rat.* PHARMACOL BIOCHEM BEHAV 47(2) 345-349, 1994.—Female rats with continuous access to water and 6% ethanol were given bilateral ventral striatal 6-OHDA infusions, which induced pronounced striatal depletions of dopamine. The postoperative ethanol consumption of these rats was not significantly affected in comparison to vehicle-infused controls. In a second experiment, female rats received escalating doses of d-amphetamine over a 5-week period (from 1 to 9 mg/kg/injection). Control females were given saline injections. Following a 3-month drug-free interval, the females were given access to ethanol, the concentration of which was gradually increased from 2% to 12% with weekly intervals. Amphetamine-sensitized rats consumed significantly more alcohol than the saline-treated controls. Taken together, these results suggest that striatal dopaminergic mechanisms, while not necessary for basal ethanol drinking, can facilitate alcohol drinking.

6-OHDA Dopamine Ethanol Amphetamine Ventral striatum Nucleus accumbens Alcohol preference Sensitization

A GROWING body of evidence suggests that mesolimbic dopamine (DA) mechanisms participate importantly in the control of processes related to incentive motivation, appetitive behaviour, and reward (9,14,26,33,39). Given this role for normal behaviour, it may be no coincidence that current animal research on the neurobiology of drug addiction also recognizes the mesolimbic DA system as an important target for several drugs of abuse (40,41). For example, psychostimulants, opioids, and nicotine increase DA release in the ventral striatum (7), whereas striatal lesions alter the self-administration of such compounds [reviewed by (20,22)].

We here report two experiments in the rat that attempted to assess the importance of ventral striatal DA mechanisms for the voluntary intake of ethanol, which, like opioids and psychostimulants, enhances the release of DA in the nucleus accumbens (11,16,42). The first experiment examined the effect of interfering with DA transmission in the ventral striatum, using local infusions of the neurotoxin 6-hydroxydopamine (6-OHDA). Previous studies on this topic have not given consistent results, research workers finding increase (31), decrease (29), or no effect (19) on ethanol intake.

The second experiment examined whether recurrent experience with amphetamine (AMPH) alters ethanol drinking in the rat. The rationale behind this study was based on the observation that repeated exposure to amphetamine progressively sensitizes rats to its acute behavioural and neurochemical effects [reviewed by (18,34)]. For example, AMPH-sensitized rats given a low dose of AMPH display intense stereotyped sniffing and gnawing behaviours rather than locomotor hyperactivity (35). They also show an enhanced DA response to AMPH in the ventral striatum (35). If mesolimbic DA mechanisms indeed modulate ethanol intake, then one would expect drinking to change following AMPH-induced sensitization of ventral striatal DA neurotransmission.

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METHOD

Experiment 1: Ethanol Intake Following Striatal 6-OHDA Lesions

Subjects were 21 female Wistar rats purchased from Möllegaard (Denmark) and weighing about 200 g at the start of the experiment. They were group housed in cages (Makrolon 4) with free access to food pellets (Ewos 34) and water. The colony room was illuminated between 10:00 p.m. and 10:00 a.m., the room temperature being about 22°C. Rats were given 2 weeks to adapt to our laboratory conditions before the experiment began.

During a 2-week period, rats were gradually familiarized to ethanol by giving them access to a bottle containing 2% (v/v) ethanol (0.5 week), 4% ethanol (1 week), and 6% ethanol (0.5 week). A water bottle was always available. Animals were then individually housed in clear plastic cages (45 × 30 × 16 cm) where they had continuous access to two 300-ml bottles with ball valve spouts (ALAB) to minimize spillage and evaporation. One bottle contained a 6% (v/v) ethanol solution and the other tapwater. The baseline intake of ethanol and water was recorded by weighing the bottles twice weekly (Mondays and Thursdays) for 3 weeks. On the basis of their individual ethanol preference (ethanol intake in percent of total fluid intake), subjects were then divided into two matching groups—6-OHDA (n = 10) and vehicle (n = 12)—and taken for surgery.

Rats were anesthetized with Brietal (sodium methohexithal, Eli Lilly & Co., Indianapolis, IN; 10–15 mg/rat) and fixed in a Kopf stereotaxic instrument (Kopf, Topanga, CA). 6-OHDA HCl (Sigma Chemical Co., St. Louis, MO) was infused through a stainless steel cannula (outer diameter 0.25 mm) using a CMA100 microinjection pump (CMA AB, Stockholm, Sweden). Two microliters of 6-OHDA (4 μg/μl of the base) was given over 4 min and the cannula was left in situ for an additional 3 min before being retracted from the brain. Thirty minutes before the infusion, each rat received IP injections of the noradrenergic uptake inhibitor desipramine (25 mg/kg) and the MAO inhibitor pargyline (50 mg/kg). These compounds minimize destruction of noradrenaline neurons and potentiate the neurotoxic action of 6-OHDA, respectively (17,43). The following coordinates were employed (30): 1.6 mm anterior to bregma, 1.5 mm lateral to midline, 8.3 mm below the skull. Control animals received vehicle (0.1% ascorbic acid in saline) at these sites after having been pretreated with desipramine and pargyline. After surgery, females were returned to their home cages and the postoperative consumption of 6% ethanol and water was monitored for 3 additional weeks.

Following completion of the behavioural studies, 10 6-OHDA- and 5 sham-operated rats were selected at random for neurochemical determinations. Following decapitation, brains were rapidly removed from the skull and the following areas were dissected out: dorsal striatum (caudate putamen), ventral striatum (nucleus accumbens, olfactory tubercle), hippocampus, and cortex. The tissue was stored in −70°C until the levels of DA, noradrenaline (NA), and 5-hydroxytryptamine (5-HT) were determined using high-performance liquid chromatography with electrochemical detection (36).

The data are presented as mean ± SE. Behavioural group differences were assessed by the Mann–Whitney U-test and the neurochemical data with Student's t-tests (Apple StatView software). Two-tailed significance levels were used.

Experiment 2: Ethanol Intake Following d-*Amphetamine Sensitization*

Subjects were 21 female Wistar rats (Möllegaard Inc., Denmark) weighing about 200 g at the start of the experiment. They were maintained under the same laboratory conditions as described in Experiment 1.

Two weeks after the arrival in the laboratory, each animal was injected SC twice daily with either 0.9% saline (SAL) (n = 10) or d-amphetamine sulfate (n = 11; Sigma). The two injections, separated by about 6 h, were given on weekdays (not on weekends) for 5 consecutive weeks. Rats in the drug treatment group received the following AMPH doses/injection, adapted and modified from Robinson et al. (35): days 1–2, 1 mg/kg; days 3–5, 2 mg/kg; day 6, 3 mg/kg; days 7–11, 4 mg/kg; days 12–15, 5 mg/kg; day 16, 6 mg/kg; days 17–20, 7 mg/kg; day 21, 8 mg/kg; days 22–25, 9 mg/kg. The doses are expressed as the salt and were administered as 1 ml/kg.

Three months after the last injection, females were housed individually and given continuous access to two 300-ml bottles with ball valve spouts, one bottle containing an ethanol solution and the other plain water. The ethanol concentration was gradually increased with 7-day intervals in the following order: week 1, 2% (v/v); week 2, 4%; week 3, 6%; week 4, 8%;

TABLE 1

LEVELS OF DOPAMINE, NORADRENALINE, AND SEROTONIN IN RATS INFUSED WITH 6-OHDA IN THE VENTRAL STRIATUM

	Ventral Striatum	Dorsal Striatum	Cortex	Hippocampus
Dopamine				
6-OHDA	56.3 ± 7.7*	688.4 ± 171.3*	44.4 ± 12.7*	17.4 ± 1.0†
Vehicle	1530.0 ± 10.4	3144.2 ± 13.8	314.4 ± 40.7	21.8 ± 0.5
Noradrenaline				
6-OHDA	502.5 ± 18.2	41.2 ± 4.3*	241.7 ± 21.5	286.2 ± 19.4
Vehicle	511.8 ± 5.5	96.0 ± 13.5	277.2 ± 23.8	292.2 ± 22.8
Serotonin				
6-OHDA	644.0 ± 41.0†	556.0 ± 58.0†	248.9 ± 42.5‡	137.3 ± 14.4*
Vehicle	847.5 ± 38.2	869.4 ± 26.0	378.7 ± 22.9	251.8 ± 15.6

Values are ng/g tissue (mean ± SE).
*$p < 0.001$; †$p < 0.001$; ‡$p < 0.05$ vs. vehicle (Student's t-test).

TABLE 2

BEHAVIOURAL PARAMETERS (MEAN ± SE) IN 6-OHDA- OR VEHICLE-INFUSED RATS DURING THE 3-WEEK POSTOPERATIVE PERIOD

	Ethanol Intake	Water Intake	Total Fluid Intake	Food Intake	Body Weight
6-OHDA	2.9 ± 0.3	17.6 ± 3.7	77.7 ± 7.7*	62.5 ± 4.8	240.3 ± 7.5*
Vehicle	4.0 ± 0.3	32.1 ± 8.3	115.7 ± 5.4	72.8 ± 2.4	267.6 ± 4.1

The intakes of fluids and food are expressed as g/kg/day.

*$p < 0.003$ vs. vehicle (the pre− postoperative difference scores were compared between the two groups by Mann-Whitney U test).

week 5, 10%; and week 6, 12%. The consumption of ethanol and water was measured by weighing the bottles twice a week. The data were analyzed with two-tailed Mann-Whitney U-tests.

RESULTS

Experiment 1: Ethanol Intake Following Striatal 6-OHDA Lesions

On the basis of the neurochemical measurements, one 6-OHDA rat was excluded. In the remaining nine experimental females, DA levels were reduced to less than 4% of normal in the ventral striatum (Table 1). There were also significant, but less dramatic, DA depletions in the other areas sampled, including the dorsal striatum (22% of control levels), where NA levels were also lowered. The levels of 5-HT were below normal (55–76%) in all brain regions.

Table 2 shows that the 6-OHDA treatment significantly decreased body weight and reduced total fluid (ethanol + water) intake during the postoperative period. None of the other items, such as ethanol preference or ethanol, water, and food intakes, were significantly altered.

Experiment 2: Ethanol Intake Following d-*Amphetamine Sensitization*

At the end of the 5-week drug treatment period, AMPH-treated rats weighed about 15 g less that SAL-injected females. This difference in body weight disappeared during the ensuing 3-month wash-out period, and no group difference in body weight was recorded during the 5 weeks of ethanol presentation.

Figure 1 shows ethanol intake in AMPH- and SAL-treated rats. For the statistical analysis, the total intake of ethanol over all concentrations was estimated for each rat and the mean intake (expressed as g/kg/day) was calculated. Comparison of these means (AMPH, 19.3 ± 2.4; SAL, 11.9 ± 2.4) revealed that AMPH-treated animals consumed more alcohol than SAL-treated controls ($p < 0.02$). Fluid intakes were subsequently analyzed for the low (2–6%) and high (8–12%) ethanol concentrations. The enhanced ethanol consumption of AMPH-treated rats was evident in the 8–12% range (AMPH, 3.5 ± 0.6; SAL, 1.9 ± 0.4; $p < 0.05$). The groups did not differ in the 2–6% range (AMPH, 2.7 ± 0.2; SAL, 2.1 ± 0.3). There were no statistically significant differences between the groups in mean total fluid intake (expressed as ml/kg/day) either in the 2–6% (AMPH, 102.8 ± 5.0; SAL, 94.0 ± 6.1) or 8–12% range (AMPH, 97.2 ± 11.0; SAL, 82.0 ± 3.5). Therefore, the increased ethanol consumption observed in the AMPH group was not simply a consequence of an enhanced total fluid intake.

DISCUSSION

Interfering with DA transmission by means of DA receptor antagonists or 6-OHDA lesions has been reported either to enhance, depress, or exert no effect on ethanol intake in rats (3,15,19,23,24,29,31). In line with some of these studies [(3, 19,24); see also (2,6,25)], we failed in the present study to observe any consistent effect of striatal 6-OHDA infusions despite the fact that the DA levels in our animals were depleted by 95% in the ventral striatum and by 78% in the dorsal striatum. However, the lesions did lower total fluid intake and body weight. Considering the importance of the nigrostriatal

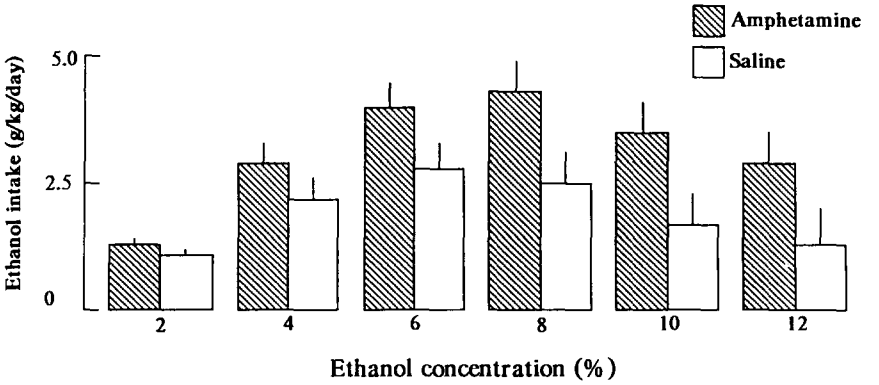

FIG. 1. Consumption of ethanol (mean ± SE) in rats exposed to escalating doses of d-amphetamine 3 months before being given access to ethanol solutions of varying concentrations.

DA system for feeding and drinking [reviewed by (38)], it is likely that the relatively large dorsal striatal DA depletions observed in our experimental rats account for the reductions in these parameters.

It should be noted that there were moderate, although significant, depletions of 5-HT in 6-OHDA-infused animals. Because decreased 5-HT neurotransmission can facilitate ethanol drinking in rats [reviewed by (10)], we cannot exclude the possibility that the concurrent 6-OHDA-induced 5-HT deficiency cancelled or masked any suppressive effect of DA lesions on ethanol consumption. Indeed, it has been shown in other contexts that lesions of non-DA transmitter systems modify the behavioural effects of DA depletions (37).

Given these qualifications with regard to the neurochemical specificity of our lesion data, we have no ready explanation as to why different groups of investigators arrive at so disparate conclusions concerning the effects of neurotoxin or pharmacological DA blockade on ethanol drinking. However, it should be noted that, in contrast to the present study, much research in this field is conducted on rats selectively bred for high ethanol intake (21,23,28). It is conceivable that different lines of such high-preferring animals consume large amounts of alcohol for distinct neurochemical reasons and hence different strains of rats may differ in their sensitivity to various neurochemical interventions. Hereditary neurochemical strain differences, as well as factors such as age, sex, and hormonal status [reviewed by (8)], may partly determine the behavioural vulnerability to DA blockade.

A number of studies have shown that repeated administration of AMPH progressively sensitizes rats' behavioural responses not only to AMPH itself but also to other psychostimulants and to opioids [reviewed by (18,34)]. In view of such examples of cross-sensitization between different classes of drugs of abuse, the second experiment assessed the effect of AMPH sensitization on voluntary intake of ethanol. It was found that rats exposed over the course of 5 weeks to escalating doses of AMPH consumed significantly more alcohol than controls when tested 3 months after the last injection. It is clear, then, that repeated administration of AMPH can induce persistent alterations in the neuroendocrine mechanisms mediating ethanol consumption in the rat.

An AMPH regimen akin to the one employed here has been shown to dramatically enhance the extracellular overflow of DA following an acute AMPH challenge, while not altering basal DA release (35). Like AMPH, ethanol also increases ventral striatal DA release (16,42) and it may well be, then, that enhanced alcohol-induced DA release in the accumbens underlies the increased drinking of AMPH-sensitized rats. Another interpretation relates to recent work showing that corticosterone, the major glucocorticoid in the rat, regulates both AMPH sensitization and ethanol drinking in the rat. For instance, treatments that induce abnormally low levels of circulating corticosterone attenuate AMPH sensitization (5,32) and selectively depress ethanol consumption (12,13,27). It is possible, therefore, that repeated exposure to AMPH, just like repeated exposure to stress, is associated with enduring changes in the hypothalamo-pituitary-adrenal axis (1,6) that promote subsequent ethanol intake.

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