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Ethanol Intake Increases during Continuous Administration of Amphetamine and Nicotine, but not Several Other Drugs

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POTTHOFF, A. D., G. ELLISON AND L. NELSON. *Ethanol intake increases during continuous administration of amphetamine and nicotine, but not several other drugs.* PHARMACOL BIOCHEM BEHAV 18(4) 489–493, 1983.— Groups of rats, acclimated to drinking both water and 10% v/v ethanol were implanted with a variety of slow-release devices containing d-amphetamine (d-amp), nicotine, caffeine, phencyclidine (PCP), secobarbital, LSD, mescaline or haloperidol. Ethanol intake was elevated only during treatment with d-amp or nicotine; none of the other drugs affected ethanol consumption even though the amounts of all drugs released were pharmacologically sufficient to affect behavior. Nicotine treated rats were not simply seeking calories provided by the EtOH solution, since nicotine treatment did not enhance intake of a distinctively flavored solution isocaloric to 10% ethanol. These results support a self-medication model of ethanol intake.

Ethanol intake d-Amphetamine Nicotine Caffeine Phencyclydine Secobarbital LSD Mescaline Haloperidol Self-medication

RATS implanted with continuous slow-release d-amphetamine (d-amp) pellets and offered continuous access to water, 10% EtOH, and food dramatically increase their voluntary intake of ethanol; this effect does not occur if isocaloric glucose solutions or other flavored solutions are offered in lieu of the EtOH [15]. In order to obtain this result, a special experimental paradigm must be used involving a period between the time when the animal first is administered the d-amp and can again drink EtOH so as to minimize the role of taste aversions.

These results are consistent with a self-medication model. That is, the continuous d-amp treatment induces chronic hyperactivity [14,16] and the subjects drank more EtOH as a means of antagonizing this chronic hyperactivity. Yet some alternative explanations have not been investigated. It is possible that the general stressing effects of continuous treatment with any drug, not just stimulants as stipulated by the self-medication hypothesis, would induce increases in EtOH intake. Also, many researchers have hypothesized that unique interactions between catecholamines and EtOH can result in the production of compounds with opioid-like activity [2,3] or to permanent increases in EtOH consumption [13]. The increased intake following continuous d-amp could thus be the result of a unique interaction between EtOH and the prolonged modification of the central adrenergic neuronal systems produced by d-amp.

The present experiments were designed to test these possibilities by assessing the effects of a variety of other continuously administered psychoactive agents on EtOH consumption. The drugs tested included d-amp, nicotine, caffeine, phencyclidine (PCP), secobarbital, LSD, mescaline, and haloperidol.

METHOD

Subjects and procedures. Female albino rats (Simonsen Laboratories, Gilroy, Ca), initially weighing 250–300 g, were individually housed under constant lighting with ad lib access to Purina pellets, tap water and 10% (v/v) EtOH. Both fluids were presented in calibrated drinking tubes (Wahman). Every third day EtOH and water intake was measured and the positions of the water and EtOH tubes were switched.

Ten groups of six subjects each were acclimated to drinking EtOH for a minimum of 30 days. Both 10% (v/v) EtOH and water were continuously available during this period. Acclimation was continued until baseline intake of EtOH and water was stable, within ± 5 ml/day and having no discernable trends, over 12 days. Subjects were then implanted subcutaneously, under local lidocaine anesthesia, with continuous slow-release pellets. During the following six days all rats had access to water alone. EtOH was then returned, data was collected for 24 days, and the pellets were removed.

Two groups were treated with continuous slow-release d-amp. Each group represents an independent replication of the original finding [15]. Seven independent groups were treated with continuous slow-release nicotine, caffeine, PCP, secobarbital, LDS, mescaline, and haloperidol, respectively.

TABLE 1

BASELINE AND EXPERIMENTAL RATES OF FLUID INTAKE

Drug	No. of Subjects	Baseline Intake ETOH ml/day	Baseline Intake WATER ± s.e.m.	Treatment Intake ETOH ml/day	Treatment Intake WATER ± s.e.m.
Amphetamine	12	10.2 ± 1.9	15.5 ± 1.7	20.6 ± 2.3†	12.6 ± 2.4*
Nicotine	6	8.1 ± 1.1	11.1 ± 1.6	16.7 ± 2.0†	3.9 ± 4.2†
Caffeine	6	9.4 ± 1.8	15.9 ± 3.6	12.6 ± 3.2	23.2 ± 4.1
PCP	6	11.9 ± 1.1	13.3 ± 0.9	15.4 ± 2.4	8.7 ± 1.9
Secobarbital	6	10.3 ± 0.9	12.4 ± 1.6	12.3 ± 1.3	11.1 ± 2.3
LSD	6	12.8 ± 1.0	13.0 ± 1.8	14.4 ± 1.4	11.6 ± 2.1
Mescaline	6	8.6 ± 1.7	13.5 ± 2.2	11.6 ± 3.1	15.1 ± 3.0
Haloperidol	6	8.3 ± 0.9	11.8 ± 1.7	12.2 ± 0.9	5.0 ± 1.7*

*$p<0.05$.
†$p<0.01$.

Implantable Continuous Drug-releasing Devices

Silicone Pellets. d-Amp, PCP, and mescaline were administered using silastic slow-release pellets constructed as described previously [14]. A 45 mm-long polyethylene cylinder, with an inside diameter of 5 mm and two 1.3 mm-diameter holes near its middle, was enclosed in 1.59 mm-thick silastic tubing, filled with 0.7 ml of drug base in vehicle and capped at each end with silastic polymer. The continuous slow-release d-amp, PCP and mescaline pellets contained 65, 71 and 165 mg of drug base, respectively, suspended in 0.7 ml polyethyleneglycol (PEG), and released an average of 1.1, 0.98, and 0.55 mg/day, respectively, over 30 days.

The secobarbital and haloperidol pellets represent a modification of the prototype pellet, in which the polyethylene cylinder has been omitted. Thus, 45 mm-long, 1.59 mm-thick, 4.76 mm I.D., 7.94 mm O.D. silastic tubing, was filled and capped at each end with silastic polymer. The secobarbital pellet contained 800 mg base suspended in 0.8 ml PEG. The haloperidol pellet contained 100 mg in 0.8 ml lactic acid. The secobarbital and haloperidol pellets released 6.52 and 1.24 mg/day, respectively, over 30 days.

Nicotine was administered via implantable glass reservoirs constructed according to methods previously described [6]. Glass capsules, 20 mm long, 4 mm I.D., filled with 0.2 ml nicotine base (Sigma) and capped with silastic polymer, were immersed in distilled water for 72 hours, then implanted subcutaneously. These nicotine pellets have been reported to release 3.4 mg/day.

Caffeine was administered via a refillable silastic pillow as described previously [4]. A 64 mm × 76 mm pouch of 0.51 mm-thick silastic sheeting was sealed with silicone type A adhesive and connected to a 0.16 mm I.D. silastic tube, which served as a spout. Joints were coated with silastic polymer in order to minimize skin irritation. The pillows were implanted under sodium pentabarbital general anesthesia, filled with water and plugged with a stainless steel bong. At the beginning of the experimental period, the plug was removed and the water withdrawn via the spout using a 12 cc syringe. The water was replaced in the pillow with caffeine solution and the plug replaced. The pillows were then emptied and refilled daily during the experimental period. The drug treatment period was limited to 21 days because of severe infections in some animals. The caffeine pillows released 200 mg/day.

LSD was administered via Alzet minipumps (Model No. 2002, Alza Corp.) filled with 1.06 mg of LSD bitartrate (Sandon). A second minipump was implanted after 15 days. The minipumps released 0.1 mg/day.

Release rates for all drugs were determined by HPLC assays of pellet contents, except for minipumps, which rates are based on manufacturers' specifications. Pellets were removed from the animals 30 days after implantation, opened and soaked in methanol for several days. Release was calculated by comparing the drug content of these pellets with that from identically constructed pellets that were never implanted. HPLC assays were conducted on a Hewlett-Packard system using uv detection (254 nm).

Supplementary Experiment

When it was found that EtOH intake was significantly increased in the nicotine-treated group, an additional experiment was designed to test whether the changes in EtOH consumption were due to taste aversion to water or to the caloric content of the EtOH. A new group of six rats, habituated to consuming a distinctively flavored glucose solution (Polycose) isocaloric to 10% EtOH, was otherwise treated identically to the nicotine group, and the alterations in flavored fluid intake compared. Fresh Polycose solutions were prepared daily by dissolving the glucose polymers (Ross Laboratories, Columbus, OH) into tap water at a concentration of 0.135 g/ml, and then adding 0.12 mg/ml quinine hydrochloride. An unadulterated glucose solution would have been consumed to the exclusion of water. Previous work [15] indicated that at these concentrations approximately 40% of total fluid intake was Polycose solution.

RESULTS

Table 1 presents the mean baseline rates of water and EtOH intake prior to and during the drug administration period for all groups. Both d-amp-treated groups showed similar results. Therefore, the results of these two groups were combined for data analysis. Using paired-comparison t-tests, with each animal contributing a pre-drug and a

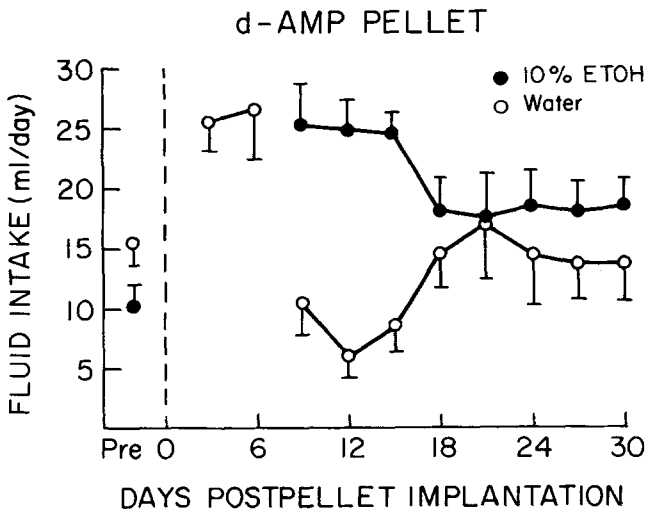

FIG. 1. EtOH and water for d-amp-treated rats in 3-day blocks. Darkened circles represent consumption of 10% v/v EtOH. Open circles represent water intake.

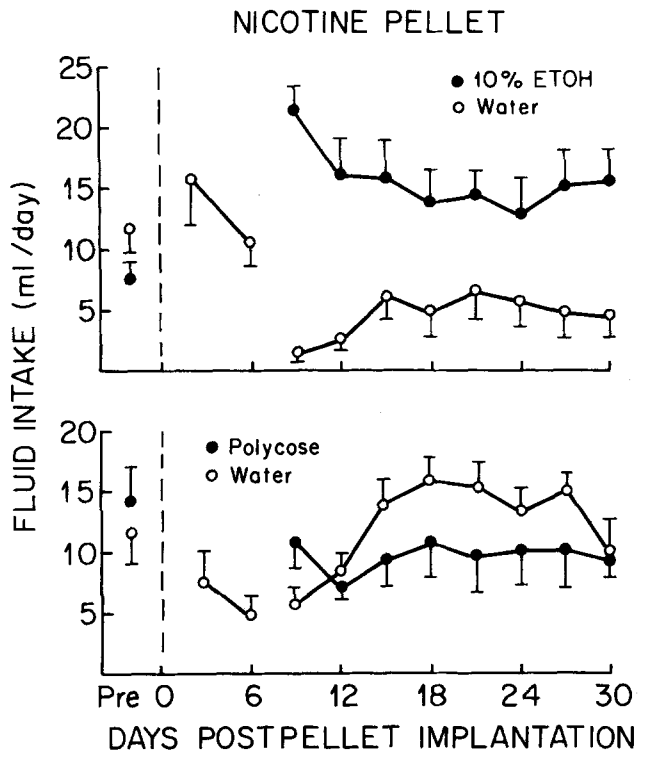

FIG. 2. Flavored fluid and water consumption in nicotine-treated rats, in three day blocks, offered either 10% EtOH or polycose and water. Darkened circles represent consumption of 10% EtOH in the upper figure and polycose intake in the lower figure. Open circles represent water consumption.

during-drug score, it was found that only the d-amp-treated groups ($t=7.87$, $p<0.001$) and the nicotine-treated groups ($t=6.01$, $p<0.01$) showed significant changes in mean EtOH intake. The d-amp-treated rats increased EtOH intake from 10.2 ml/day during baseline to 20.6 ml/day during the experimental period. The nicotine-treated rats increased EtOH consumption from 8.1 to 16.7 ml/day. Analysis of variance of EtOH, water and total fluid intake over days revealed significant differences for only the d-amp-treated and the nicotine-treated groups.

Daily EtOH drinking by the d-amp-treated group is illustrated in Fig. 1. Mean intake of EtOH (darkened circles) increased to 25.4 ml/day when the EtOH was returned. Thirty days after pellet implant, EtOH consumption was still at the elevated rate of 18.3 ml/day. Analysis of variance on changes in EtOH intake over days was significant ($F=11.46$, $p<0.001$). A posteriori comparisons by Dunnet's tests showed that mean EtOH consumption was higher on all experimental blocks than it was during baseline ($p<0.01$).

A closer analysis of the nicotine-treated group's EtOH drinking is shown in Fig. 2, top. Mean intake of EtOH (darkened circles) increased to 22.2 ml/day when the EtOH was returned. Thirty days after pellet implant EtOH consumption was still at the elevated rate of 16.6 ml/day. Analysis of variance on changes in EtOH intake over days was significant ($F=3.77$, $p=0.002$). A posteriori comparisons by Dunnet's test showed that mean EtOH consumption was higher on all experimental blocks, except days 21–24 post-implant, than it was during baseline ($p<0.05$).

Table 1 lists the baseline rate of water intake and the mean rates of water consumption during the drug treatment period, in ml/day for all groups. Alterations in water consumption were significant only for the d-amp-treated groups ($t=2.59$, $p<0.05$), the nicotine-treated group ($t=6.27$, $p<0.01$), and the haloperidol-treated group ($t=2.92$, $p<0.05$). All three groups showed decreased water intake.

A more detailed analysis of the d-amp-treated group's water drinking is shown in Fig. 1. Mean water consumption (open circles) decreased to 10.3 ml/day when the EtOH was returned. Intake was lowest during 10–12 days post implant at 5.9 ml–day, after which water consumption increased to baseline rates. Analysis of variance on changes in water intake over days was significant ($F=3.30$, $p=0.003$). A posteriori comparisons by Dunnet's tests showed that mean water consumption was significantly lower than baseline only from days 9–15 post implant ($p<0.05$).

The nicotine-treated group's water drinking is available for closer examination in Fig. 2, bottom. Mean intake of water (open circles) decreased to 1.7 ml/day when the EtOH was returned. Thirty days after pellet implantation, EtOH consumption was still up only to 4.0 ml/day. Analysis of variance on changes in water intake over days was significant ($F=4.97$, $p<0.001$). A posteriori comparisons by Dunnet's tests showed that mean water consumption was lower on all experimental blocks than it was during baseline ($p<0.05$).

For the haloperidol-treated group, water consumption decreased to 7.4 ml/day when the EtOH was returned. Intake continued to decrease and was lowest during 19–21 days post implant at 5.9 ml/day, after which water consumption increased, but did not return to baseline rates. Analysis of variance on changes in water intake over days was significant ($F=3.37$, $p=0.004$). A posteriori comparisons by Dunnet's tests showed that mean water consumption was significantly lower than baseline from days 10–30 post-implant ($p<0.05$).

T-tests were also performed to determine if any of the

drug treatments significantly altered total fluid intake. d-Amp treatment resulted in an increase of total fluid intake from 25.7 ml/day during baseline to 32.8 ml/day during the experimental period ($t=4.27$, 11 *d.f.*, $p<0.01$). Caffeine treatment also significantly increased total fluid intake. Baseline intake of 20.6 ml/day was raised to 25.2 ml/day ($t=2.87$, 5 *d.f.*, $p<0.05$). In addition, mescaline treatment elevated total fluid consumption from 22.1 ml/day during baseline to 26.7 ml/day during the experimental period ($t=4.16$, 5 *d.f.*, $p<0.01$).

The overall effects of continuous nicotine treatment on Polycose intake and water intake of Polycose-drinking rats are also listed in Table 1. Neither mean Polycose intake nor mean water intake were altered significantly. Figures 2a and 2b illustrate comparisons of EtOH-drinking and Polycose-drinking rats. EtOH-drinking nicotine-treated rats consumed significantly more flavored fluid than did the Polycose-drinking nicotine-treated rats ($F=8.83$, $p=0.014$). There was neither a significant effect of days nor a significant days-by-fluid interaction. However, there was a significant days-by-fluid interaction when water consumption by the two groups was analyzed ($F=4.25$, $p<0.001$). Tests for simple main effects revealed that water consumption changes significantly over days for both the EtOH-drinking rats ($F=6.64$, $p<0.001$) and the Polycose-drinking rats ($F=46.9$, $p<0.001$). The EtOH-drinking rats also consumed significantly less water than the Polycose-drinking from days 13 to 30 post-implant (F ranged from 4.55 to 17.8, p ranged from 0.03 to 0.001).

DISCUSSION

These results replicate our previous report that rats administered continuous d-amp greatly increase their consumption of 10% EtOH [15,16]. In the present experiment a variety of other drugs were also tested using the same paradigm to determine whether they would also induce increases in EtOH intake. Of all of the drugs tested, only nicotine and d-amp produce significant alterations in EtOH consumption.

The increased EtOH intake induced by continuous administration of these two drugs was neither due to taste aversions to water nor to the caloric content of the EtOH solution, as the rats administered these same drugs but offered a distinctively flavored solution isocaloric to 10% EtOH did not show significantly increased flavored fluid intake. We have previously reported that a control group treated with an inert pellet, containing only PEG which does not diffuse across the silastic barrier, and exposed to the same schedule of EtOH availability as the experimental groups in the present experiment does not show significantly altered EtOH intake [15].

Rats treated with continuous phencyclidine, secobarbital, mescaline, LSD or haloperidol did not show significantly altered EtOH intake. The failure of these compounds to alter EtOH intake significantly is probably not due to a failure to deliver pharmacologically effective quantities of these agents. In a previous study from our laboratory [5], the hallucinogens LSD and mescaline were administered using the same dose regimens as in the present study and were found to cause appreciable alterations in social and other behaviors. The haloperidol pellet used in the present experiment significantly lowered water consumption. In other experiments we have found that implantation of these haloperidol pellets substantially decreases photocell crossings. The secobarbital treated animals were inactive and docile when handled. The PCP-treated animals showed transient adipsia and marked ataxia, followed by a period of hyperactivity accompanied by a peculiar dysphagia, in which the rats would break up their food pellets but not consume them.

Our findings that these drugs were ineffective in inducing increased EtOH consumption might be criticized on the basis of the fact that only one dosage of each drug was administered. However, when continuous, low-level drugs are administered over prolonged periods of time, precise drug dosage does not appear to be extremely critical. We have obtained similarly increased EtOH consumption using d-amp pellets which vary by as much as 200% in drug output. Furthermore, results identical to those reported in this paper were obtained using a weaker haloperidol pellet.

It may also be argued that the enhanced EtOH intake was only part of a general increase in fluid intake. However, the groups which demonstrated significantly elevated EtOH intake were selective in their increased fluid consumption. The d-amp-treated rats actually showed a significant decrease in water intake. The nicotine-treated-group did not show significant increases for total fluid intake, but did display significantly elevated EtOH consumption. In addition, both the caffeine-treated rats and the mescaline-treated rats showed significantly increased total fluid intake, but did not show significantly increased EtOH intake. Thus, there was no simple relationship between significant elevation in total fluid intake and significant elevation of EtOH intake.

The attack upon the body by any pharmacologically active agent can be defined as being a stressor [18]. Yet, most drugs tested in this experiment had no significant effect on EtOH intake. Therefore, the increased EtOH intake contingent upon continuous drug treatment was not the result of generalized stress. In the present experiment, only two of a wide variety of continuously administered psychoactive agents induce significantly increased self-selection of EtOH, and both of these compounds, d-amp and nicotine, are stimulants.

Rats treated with a third stimulant, caffeine, did not significantly increase EtOH intake. However, there were major differences between this group and the other groups. The physical size of the implanted device was much larger, and only the caffeine group required general anesthesia for implantation and had to be handled daily. Perhaps most important, the caffeine-treated rats developed severe infections and slow-release devices had to be removed early. Fluid intake was highly variable for this group. Several experiments have demonstrated that caffeine added to a marginally adequate diet results in increased EtOH intake [7, 8, 17], although discrete injections reduce EtOH intake [10] of EtOH preferring rats. For these reasons, we believe that the failure of caffeine to induce significantly heightened EtOH intake in this experiment should not lead to a rejection of the hypothesis that self-medication is specific to continuously administered stimulants.

It is important to consider the central effects of the types of pharmacological agents that induce EtOH self-medication. Heightened central catecholamine turnover correlates well with hyperarousal and stress, and both d-amp [1] and nicotine [9,19] increase catecholamine release in brain tissue. Furthermore, tetrahydropapaveroline, the condensation product of dopaldehyde and dopamine, when infused chronically into the lateral ventricle causes rats to dramatically increase EtOH intake [13], and enhances release of dopamine in brain [11,12]. This suggests an intimate relation-

ship between increased EtOH self-selection and increased central catecholaminergic stimulation, and a mechanism which may underlie the self-medication effect. Stimulants such as d-amp and nicotine, by increasing the presence of catecholamine substrates available for conversion to condensation products, may facilitate the production of compounds with opioid-like activity. Whatever the mechanism, the present results indicate that the continuous administration of two centrally active stimulants lead to heightened EtOH consumption while the continuous administration of a variety of other pharmacological agents do not.

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