Pharmacology Biochemistry and Behavior, Vol. 42, pp. 187–192, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

BRIEF COMMUNICATION

Influence of Dopaminergic and Serotonergic Neurons on Intravenous Ethanol Self-Administration in the Rat

WILLIAM H. LYNESS[1] AND FORREST L. SMITH[2]

Department of Neurology, Texas Tech University Health Sciences Center, Lubbock, TX 79430

Received 23 July 1990

LYNESS, W. H. AND F. L. SMITH. *Influence of dopaminergic and serotonergic neurons on intravenous ethanol self-administration in the rat.* PHARMACOL BIOCHEM BEHAV **42**(1) 187–192, 1992.—Rats implanted with chronic indwelling intravenous catheters and allowed access to a self-administration apparatus learned to self-inject intravenous ethanol. Ethanol concentrations of 0.5, 1.0, and 2.0%, corresponding to a dose/injection of 1, 2, and 4 mg/kg, respectively, were consistently self-injected. Self-injection was not acquired or maintained with ethanol doses of 0.5 or 8 mg/kg/injection. Saline replacement of ethanol reservoirs led to marked increases in lever-pressing response in animals self-injecting 1, 2, and 4 mg/kg ethanol/injection but not with 0.5 or 8 mg/kg/injection. Neurotoxin-induced lesions of dopamine-(DA) containing neurons in nucleus accumbens septi failed to alter the acquisition or maintenance of ethanol self-injection. Pretreatment with haloperidol (0.05 and 0.1 mg/kg, SC) failed to alter hourly or daily self-injection rates. On the other hand, *p*-chlorophenylalanine pretreatment increased, while fluoxetine (2.5 and 5.0 mg/kg) administration significantly reduced, self-injected intravenous ethanol. These data suggest that ethanol is self-injected by the rat in a narrow dose range and that 5-hydroxytryptamine (5-HT), but not DA-containing neurons, subserves some function in the reinforcing or aversive affects of ethanol.

Ethanol Self-administration Haloperidol 6-Hydroxydopamine Fluoxetine

WHILE record seizures of cocaine and heroin continue to dominate the media, the menace of alcohol abuse often receives comparatively little notice. In terms of employee absenteeism, alcohol-related health problems, and loss of life, the cost of alcohol abuse in the United States is substantial (20). Preclinical studies aimed at the elucidation of the neuronal mechanisms involved in continued alcohol abuse have been hampered to a major extent by the taste aversion to alcohol in the rat. Unless the rat is trained under unusual conditions or chronically pretreated with noncontingent ethanol and made dependent, rats do not normally initiate oral ethanol intake (6, 8,15,21,25,27). These conditions complicate interpretation of experimental results. Within the last few years, strains of rats have been utilized that are alcohol preferring, that is, they have no apparent taste aversion to alcohol (8,21,25). There is some evidence that the neurochemistry of these animals is different from that of normal, non-alcohol-preferring animals (7,30).

The use of an intravenous ethanol self-administration model has two advantages. It is a more readily available alternative than specific breeds of alcohol-preferring rats and bypasses the natural taste aversion to ethanol of most rats. Since peripheral mechanisms (taste) are inoperative, pharmacologic manipulation of brain monoamine turnover or function might prove of value in the determination of the neural substrates involved in the acquisition and maintenance of alcohol self-administration. However, the intravenous ethanol self-administration model has not been extensively studied. There have been several reports suggesting that ethanol was not self-injected by rats (3,6). It would appear, however, that the dose/injection employed by these studies may have been too large. Sinden and LeMagnen (27) reported reliable ethanol self-injection in the rat with doses below 5 mg/kg/injection. Utilizing a range of ethanol concentrations, the data below suggest that rats will self-inject IV ethanol and that manipulation of serotonergic, but not dopaminergic, neurons can alter alcohol intake.

[1] To whom requests for reprints should be addressed.
[2] Current address: Department of Pharmacology and Toxicology, Medical College of Virginia, Richmond, VA 23298.

METHOD

Male Sprague-Dawley rats (Harlan Farms, Houston, TX) weighing 275–300 g were anesthetized with pentobarbital (50 mg/kg) (halothane supplements as necessary) and implanted with chronic indwelling silastic catheters (10,28,31). Rats were allowed a 10-day surgical recovery period prior to placement in the self-administration apparatus.

The self-administration apparatus consisted of cages with dimensions of 18 × 18 × 26 cm (width, height, and length, respectively), equipped with an operant lever that, when activated, delivered 200 μl/kg/infusion drug solution. The pneumatic device delivering the ethanol solutions has been described in detail elsewhere (10,28,32). Since preliminary studies indicated no potential danger of overdose, rats were left on a continuous reinforcement schedule (FR-1) throughout the test sessions. Test sessions were 8 h in duration (0900–1700 h). A count of the daily number of lever presses was maintained using electromechanical counters and event recorders (Cole-Parmer, Chicago, IL). In addition, rats had free access to water during the test sessions.

Ethanol solutions were made fresh daily by diluting 95% ethanol in sterile 0.9% saline (Abbott, Skokie, IL). The injected alcohol solutions ranged from 0.5% [v/v, (1 mg/kg)] to 4.0% (8 mg/kg). Haloperidol was diluted from injectable preparations (McNeil Pharmaceuticals, Fort Washington, PA). Solutions containing *p*-chlorophenylalanine methyl ester (PCPA; Sigma Chemical, St. Louis, MO) and desipramine hydrochloride (Merrell Dow, Cincinnati, OH) were dissolved in water. PCPA was administered as a total dose of 320 mg/kg, given as four separate 80-mg/kg doses; each dosing was separated by 2 h. Fluoxetine was dissolved in physiologic saline prior to injection.

Bilateral destruction of dopamine- (DA) containing nerve terminals in nucleus accumbens septi were performed by microinjections of 6-hydroxydopamine (6-OHDA; 4 μg free base) in a volume of 1 μl. The compound, as hydrochloride salt, was purchased from Sigma (St. Louis, MO). The 1-μl volume was infused over a 4-min period and the injection cannula left in place an additional 4 min before removal. Rats were pretreated 1 h prior to 6-OHDA infusion with 25 mg/kg desipramine (Merrell Dow). Control animals (sham lesions) were likewise treated with desipramine but stereotaxically injected with vehicle (0.1 mg/ml ascorbic acid in 0.9% saline). The stereotaxic coordinates used were those of Pellegrino and Cushman (24): A 3.4, L ± 1.7, V −7.2. Injections were made through 30-ga stainless steel tubing. All rats in these experiments had IV cannulae implanted immediately after the stereotaxic injections and at least 10 days were allowed for recovery before self-administration studies began.

Each rat was allowed access to only one dose of ethanol and all received saline on day 10 (data presented in Fig. 1). Rats treated with PCPA, fluoxetine, or 6-OHDA-induced lesions of nucleus accumbens represent different groups of rats.

Daily ethanol self-administration was analyzed using repeated-measures analysis of variance (ANOVA) to determine differences in intake due to ethanol dose and surgical treatments. One-way ANOVA followed by the Scheffe *F*-test compared the effect of ethanol dose on pooled responses during the course of the study. ANOVA followed by the Scheffe *F*-test examined the effect of noncontingently administered drugs on ethanol intake compared with the day before and day after ethanol self-administration responding.

At the end of the self-injection trials, 6-OHDA- or vehicle-pretreated rats were sacrificed and brains immediately removed, frozen on dry ice, and later sectioned on a freezing microtome. Tissue punches from nucleus accumbens, adjacent striatum, and medial prefrontal cortex were taken as previously described (10), homogenized in 0.2 N perchloric acid, and the concentrations of DA, norepinephrine (NE), and 5-hydroxytryptamine (5-HT) ascertained using high-performance liquid chromatography (HPLC) techniques (10,17).

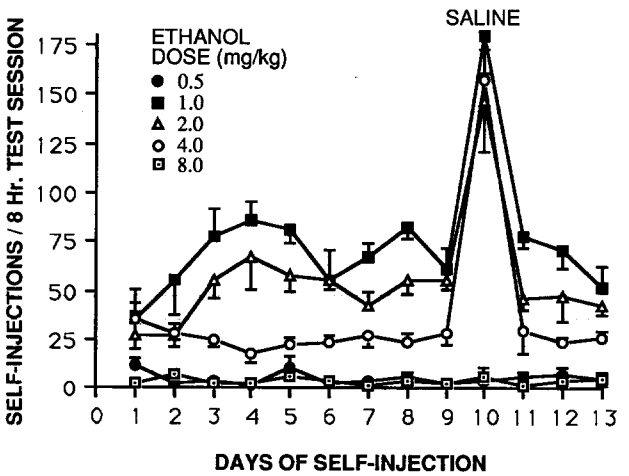

FIG. 1. Influence of dose per injection and saline substitution on ethanol self-administration. Rats (four per group) were allowed to self-administer IV ethanol as described, with the dose per injection range of 0.5–8.0 mg/kg. The number of self-injections per 8-h test session is shown (mean ± SEM). The key (top left) indicates the training and maintenance dose employed. On day 10 of the study, ethanol (all doses) was substituted by saline. Statistical comparisons were made using ANOVA with the Scheffe *F*-test.

RESULTS

Initiation of Self-Administration Behavior

Animals with no previous intravenous self-administration experience acquired stable patterns of ethanol self-injection at a fairly rapid rate (Fig. 1). Two-factor repeated-measures ANOVA demonstrated a significant ethanol dose effect on self-administration during the course of the study, $F(4, 15) = 151.4, p < 0.01$. Over the time course of these studies, rats did not appear to alter their daily dose of ethanol appreciably unless the ethanol was replaced with saline [(day 10), see below; $F(11, 165) = 1.82, p > 0.05$]. With the exception of animals allowed access to a drug reservoir containing 0.5 and 8.0 mg/kg/injection, the patterns of ethanol self-injection demonstrated a regularity with respect to the time between injections. For example, a representative rat receiving 4 mg/kg (day 7) averaged 17.36 ± 1.21 min (mean ± SEM) between injections ($n = 27$). A rat self-injecting 2 mg/kg ethanol averaged 8.92 ± 0.44 min between injections (day 7; $n = 52$) and a rat trained to self-inject 1 mg/kg IV ethanol averaged 5.65 ± 0.11 min between injections ($n = 85$). Rats allowed access to 1, 2, or 4 mg/kg/injection ethanol are more active at lever pressing than drug-naive animals allowed access to saline self-injection (range during an 8-h test session: 0–12 lever presses). It is well known that saline self-injection is neither maintained in drug-naive rats nor readily initiated.

Excluding day 10, in which ethanol reservoirs were re-

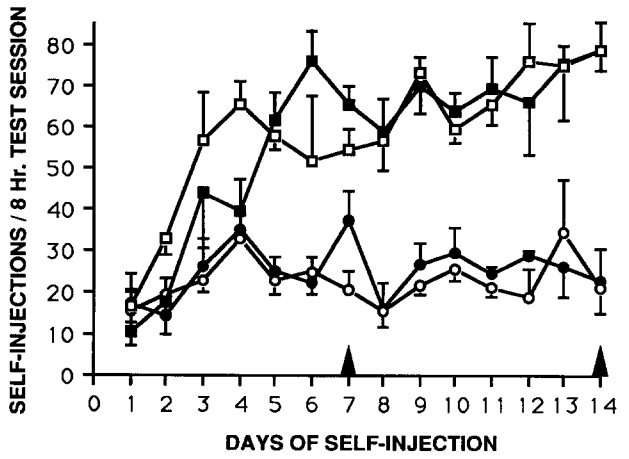

FIG. 2. Effects of 6-OHDA lesions or vehicle injections into nucleus accumbens septi and the administration of haloperidol on ethanol self-administration. Groups of four rats were stereotaxically injected with 6-OHDA or vehicle into nucleus accumbens septi and allowed to self-inject either 1.0 or 4.0 mg/kg/injection ethanol. Values represent the mean ± SEM of these results. Haloperidol was administered on day 7 (0.05 mg/kg) and on day 14 (0.10 mg/kg) to all animals. Statistical comparisons were made using ANOVA followed by the Scheffe *F*-test. Symbols: squares, 1.0 mg/kg/injection—(□), vehicle-injected rats, (■), 6-OHDA-treated rats; circles, 4.0 mg/kg/injection—(○) vehicle-injected rats, (●), 6-OHDA-treated rats.

placed with saline, a significant interaction occurred between ethanol dose and days. This was due to fluctuations in ethanol intake during the acquisition phase of training on days 1-4 for those rats self-injecting 1.0, 2.0, and 4.0 mg/kg/injection ethanol doses, $F(44, 165) = 1.73$, $p > 0.01$. Pooling the values of each dose of ethanol over the entire study, one-way ANOVA followed by the Scheffe *F*-test indicated a significant dose-related effect on the number of self-injections, $F(4, 235) = 163.4$, $p < 0.01$. Daily ethanol consumption was highest in rats self-injecting the 1.0-mg/kg/injection dose ($p < 0.01$), followed by the 2.0- and 4.0-mg/kg/injection doses ($p < 0.01$). Daily self-injection for the lowest (0.5 mg/kg/injection) and the highest (8.0 mg/kg/injection) ethanol doses were significantly lower than rats self-injecting either the 1.0-, 2.0-, or 4.0-mg/kg/injection doses ($p < 0.01$).

When ethanol self-injection appeared stable, ethanol reservoirs were replaced with ones containing saline (day 10). ANOVA followed by the Scheffe *F*-test, comparing days 9 and 11 responding with day 10 saline replacement, demonstrated that rats self-injecting 1.0 mg/kg/injection, $F(2, 9) = 21.8$, $p < 0.01$, 2.0 mg/kg/injection, $F(2, 9) = 12.9$, $p < 0.01$, and 4.0 mg/kg/injection, $F(2, 9) = 9.7$, $p < 0.01$, significantly increased their lever-pressing activity on day 10 by as much as sixfold ($p < 0.01$). When ethanol solutions were reinstated for the next 8-h test session (day 11), lever-pressing activity returned to presaline replacement values (day 9 vs. day 11: $p > 0.05$). Replacement of the ethanol reservoir with one containing saline did not alter responding in rats exposed to 0.5, $F(2, 9) = 0.54$, $p > 0.05$, and 8.0 mg/kg/injection ethanol, $F(2, 9) = 0.99$, $p > 0.05$, rats in which ethanol self-administration was not evidenced.

Lack of Influence of DA-Containing Neurons

Groups of four individual 6-OHDA-pretreated or sham-lesioned rats having no self-administration experience were allowed access to the self-administration apparatus with drug reservoirs containing either 1 or 4 mg/kg/injection ethanol (Fig. 2). Three-factor repeated-measures ANOVA revealed a significant dose effect between rats self-injecting 1.0 and 4.0 mg/kg/injection ethanol, $F(1, 8) = 224.90$, $p < 0.01$. There was a significant interaction between ethanol dose and days of self-injection represented by the acquisition phase of responding [days 1-4, $F(13, 104) = 6.13$, $p < 0.01$]. It was observed that there were no differences between 6-OHDA-lesioned rats compared to sham-lesioned rats in daily intake patterns at either ethanol dose, $F(13, 104) = 1.1$, $p > 0.05$. One 6-OHDA-lesioned rat, however (4.0-mg/kg/injection group), failed to initiate self-administration for reasons presumed to be related to cannula failure. The data pertaining to this animal were removed from analyses.

The dopamine receptor antagonist haloperidol was administered to all rats 2 h prior to placement in the self-injection apparatus on day 7 of the study (0.05 mg/kg, SC) and on day 14 (0.1 mg/kg, SC; Fig. 2). ANOVA followed by the Scheffe *F*-test comparing days 6 and 8 responding with day 7 after 0.05 mg/kg SC haloperidol demonstrated ethanol intake patterns not significantly altered ($p > 0.05$) for the 1.0-mg/kg/injection ethanol groups [6-OHDA lesion, $F(2, 6) = 0.049$, $p > 0.05$, sham lesion, $F(2, 6) = 1.45$, $p > 0.05$] and the 4.0-mg/kg/injection ethanol groups [6-OHDA lesion, $F(2, 6)$

TABLE 1

CONFIRMATION OF EXTENT AND LOCALIZATION OF NUCLEUS ACCUMBENS 6-OHDA LESIONS

		Monoamine Concentration (ng/mg protein)		
Brain Area	Treatment	DA	NE	5-HT
N. Accumbens	Control	73.4 ± 8.0	12.6 ± 0.6	8.7 ± 0.4
	6-OHDA	20.1 ± 3.9*	13.9 ± 1.1	9.7 ± 0.6
Striatum	Control	105.5 ± 9.8	5.8 ± 0.4	5.1 ± 0.1
	6-OHDA	126.4 ± 9.9	6.2 ± 0.5	5.1 ± 0.3
Medial prefrontal cortex	Control	3.6 ± 0.8	6.0 ± 0.7	8.1 ± 0.6
	6-OHDA	2.4 ± 0.7	5.6 ± 0.3	7.9 ± 0.2

Values represent the mean ± SEM of animals used in the previous self-administration study (Fig. 2). Statistical comparisons were made with 6-OHDA and control (sham lesioned) rats using Student's *t*-test.

*Significant differences were found ($p < 0.05$).

TABLE 2

INFLUENCE OF PCPA INJECTION OF THE INTRAVENOUS SELF-ADMINISTRATION OF ETHANOL

Day of Self-Injection					
Pre-PCPA			Post-PCPA		
Day 11	Day 12	Day 13	Day 14	Day 15	Day 16
45.8 ± 5.1	27.0 ± 8.8	22.3 ± 9.9	95.0 ± 11.7*	86.3 ± 24.3*	70.0 ± 8.0*

Values represent the mean ± SEM of self-injection per 8-h test session made in four rats trained to self-inject 2 mg/kg/injection IV ethanol. *p*-Chlorophenylalanine (320 mg/kg) was injected IP immediately after the training session on day 13.

*Significant differences ($p < 0.05$) from pre-PCPA test days.

= 1.69, $p > 0.05$, sham lesion, $F(2, 6) = 3.76$, $p > 0.05$]. In a similar fashion, comparing days 13 and 14 (0.1 mg/kg, SC, haloperidol treatment) demonstrated no significant differences in ethanol intake ($p > 0.05$) for the 1.0-mg/kg/injection ethanol groups [6-OHDA lesion, $F(1, 4) = 0.06$, $p > 0.05$, sham lesion, $F(1, 4) = 0.27$, $p > 0.05$] and the 4.0-mg/kg/injection ethanol groups [6-OHDA lesion, $F(1, 4) = 0.90$, $p > 0.05$, sham lesion, $F(1, 4) = 0.10$, $p > 0.05$]. Analyses of hourly self-injection rates (data not shown) also failed to demonstrate an effect of haloperidol pretreatment.

At the conclusion of the studies (3 days after the last IV ethanol test sessions), determinations of the extent of the lesions were performed. These data are illustrated in Table 1. Bilateral injection of 6-OHDA into nucleus accumbens resulted in 73% reductions in DA and had no effect on NE or 5-HT concentrations. The adjacent striatal tissue punches revealed no changes in monoamine content, suggesting lesions were limited in scope to nucleus accumbens. DA concentrations in medial prefrontal cortex were lower, reflecting possible damage to fibers of passage, but not statistically different from sham-lesioned rats.

Manipulation of CNS 5-HT functions were attempted using PCPA, a tryptophan hydroxylase inhibitor demonstrated to profoundly lower brain 5-HT concentrations, and the 5-HT reuptake inhibitor fluoxetine. Pretreatment of rats with PCPA reduced whole brain 5-HT by 77 ± 9% (mean ± SE; $n = 4$) 24 h after injection. This same PCPA regime led to an increased responding for 2 mg/kg IV ethanol (Table 2).

In an additional group of animals, fluoxetine (2.5 or 5.0 mg/kg) was injected IP 2 h prior to placement in the self-administration apparatus (Table 3). Fluoxetine, at both doses, significantly reduced ethanol self-injection of 1 and 4 mg/kg IV ethanol. In addition, the highest dose of fluoxetine employed (5.0 mg/kg) significantly reduced ethanol self-administration in the subsequent 8-h test session as well.

DISCUSSION

It was apparent from the data that rats quickly learned to self-inject intravenous ethanol. Ethanol must have positive reinforcing properties in the rodent since the patterns of self-administration appear stable, rats receiving ethanol consistently exhibited more lever-pressing activity than would be expected from rats receiving saline, lever-pressing activity appeared dose related, and, finally, substitution of ethanol by saline led to increased lever-pressing behavior [frustration; cf. review, (33)]. These observations are consistent with positive reinforcement associated with a drug. Ethanol self-injection only occurs, however, within a narrow window of >0.5 mg/kg/injection but less than 8 mg/kg/injection in our rats. It is conceivable that 0.5-mg/kg ethanol solutions are below the threshold for establishing a positive reinforcing effect of the

TABLE 3

INFLUENCE OF FLUOXETINE PRETREATMENT ON IV ETHANOL SELF-ADMINISTRATION

Treatment Group	Day of Self-Injection					
	Prefluoxetine			Postfluoxetine		
	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
I	66.6 ± 5.1	52.3 ± 8.4	73.0 ± 7.6	22.3 ± 7.8*	44.0 ± 8.8	70.8 ± 6.9
II	20.1 ± 6.3	26.3 ± 5.5	26.5 ± 2.1	9.0 ± 1.7*	9.3 ± 2.1*	18.5 ± 2.9

Values represent the mean ± SEM number of self-injections per 8-h test session from four rats per group. Animals in treatment Group I were trained to self-administer 1 mg/kg/injection ethanol IV and administered 2.5 mg/kg fluoxetine IP 2 h prior to placement in the self-administration apparatus. Rats in Group II were trained to self-inject 4 mg/kg ethanol and injected with 5 mg/kg IP fluoxetine on day 10 of the training schedule.

*Significant differences from the appropriate day 9 values (Student's *t*-test; $p < 0.05$).

drug. The sudden decrease in lever pressing activity at 8 mg/kg/injection led us to believe that some aversive actions of IV ethanol became operative. The strongest circumstantial evidence in support of this hypothesis came from preliminary studies in which animals trained to self-administer 1- or 4-mg/kg ethanol solutions decreased self-injection behavior dramatically when 8-mg/kg solutions are substituted for the training dose. This narrow dose window supporting self-administration was first proposed by the findings of Sinden and LeMagnen (27) and may explain the failure to observe ethanol self-administration in other studies with larger dose/injection regimens (3,6). The small dose window supporting self-administration is not altogether unusual. It does appear, however, that like morphine and the psychomotor stimulants IV ethanol does have positive reinforcing properties in the rat.

It is well established that dopaminergic and serotonergic neurons are of import in continued psychomotor stimulant self-administration. Disruption of dopaminergic pathways can reduce or abolish both cocaine and amphetamine self-administration in the rat (18,26). Noncontingent injections of dopamine agonists like apomorphine suppress response for psychomotor stimulants and the administration of dopamine receptor antagonists, in accord with the dopamine hypothesis of reward, leads to an increased response rate [cf. review, (33)]. The administration of haloperidol, but not β-blocker propranolol, reduced the subjective rating of amphetamine-induced euphoria in humans (12), strongly implicating a dopaminergic component in psychomotor stimulant positive reinforcement.

The situation in alcohol abuse studies is less than clear. It has been suggested that DA-containing neurons might participate in the positive reinforcing effects of alcohol and other drugs of abuse (34,35). Dopamine receptor antagonists have been reported to attenuate alcohol consumption (9) or to have no effect (5). Enhancement of DA receptor function has likewise been reported to decrease alcohol consumption or to have no effect. A parallel situation has been noted in studies employing lesions of DA containing ascending pathways, that is, decreased alcohol consumption (23) or no effect (2). Using a limited alcohol access paradigm, Linesman (14) demonstrated that manipulation of either D_1 or D_2 receptor function did not affect oral ethanol consumption.

Rats with substantial losses of DA within nucleus accumbens septi acquired and maintained self-injection of both 1 and 4 mg/kg/injection IV ethanol in a manner identical to sham-lesioned rats and at rates comparable to nonlesioned animals. Similarly, blockade of DA receptors with haloperidol, doses we have noted produce marked increases in *d*-amphetamine self-injection (unpublished), fail to alter IV ethanol intake. The dose of haloperidol chosen for these studies can induce 150–200% increases in striatal and nucleus accumbens dopamine metabolites, indicative of dopamine receptor blockade and compensatory increased neurotransmitter turnover. Similarly, in preliminary studies, apomorphine administration also failed to influence ethanol self-administration in the rat with the exception of high doses (>1 mg/kg, SC). These doses also produced stereotypy and it is therefore likely that the transient behavioral disruption reduced the IV ethanol self-injection for short periods. Since neither stimulation nor blockade of DA receptors or lesions of DA-containing neurons altered ethanol self-administration, it was therefore unlikely that DA-containing neurons, in loci identified as important in psychomotor stimulant self-injection, played a role in the positive reinforcing effects of ethanol in our animals.

On the other hand, manipulation of the 5-HT-containing pathways in the CNS has been shown to alter IV self-administration of the psychomotor stimulants, morphine, and the oral consumption of ethanol. Lesions of serotonergic pathways have been demonstrated to increase amphetamine self-injection (13,19) and drugs that enhance serotonergic receptor function decrease amphetamine abuse in the animal model (13,16,28,36). The influence of serotonergic neurons in the rat self-administration paradigm has recently been extended to include morphine: 5,7-dihydroxytryptamine (DHT)-induced depletions of forebrain 5-HT leading to increased morphine self-administration (29). The results with PCPA suggested that, like the opiates and psychomotor stimulants, IV ethanol self-injection was also influenced by the dynamics of 5-HT-containing neurons. The majority of publications indicate that PCPA pretreatment reduces oral ethanol consumption [cf. review, (23)]. Only one study has indicated increases in ethanol drinking (11). Studies with neurotoxins 5,6-DHT or 5,7-DHT generally indicate increases in oral ethanol consumption (23) or no change (22). The discrepancy between results in the PCPA and 5,6,-DHT/5,7-DHT studies cannot be resolved at this time. Further, it is not certain whether results can be compared between IV and oral self-administration experiments. Pretreatment of rats with fluoxetine, a 5-HT reuptake inhibitor, significantly reduced the self-injection of ethanol. This attenuation, with the exception of the 4 mg/kg/injection rats administered 5 mg/kg fluoxetine, generally lasted only 1 day. The attenuation of ethanol self-administration by fluoxetine is similar to that noted in amphetamine self-administration rats. Fluoxetine, in identical doses, can markedly reduce amphetamine self-injection but did not alter saline frustration responding (36). Further, our results are similar to those found in oral ethanol studies, where 5-HT reuptake inhibitors decrease ethanol intake (23).

There is a wealth of data supporting a role of 5-HT-containing neurons in continued alcohol consumption in both rats and humans [cf. review, (1,23)]. In both species, experiments were conducted after oral ingestion. Nevertheless, the work reported herein supports a serotonergic role in IV ethanol self-administration and further complements other works that could not substantiate a notable function of dopaminergic neurons in alcohol-induced positive reinforcement (2,4, 5,14).

In conclusion, it appears that doses of ethanol between 0.5 and 8 mg/kg IV support stable self-administration. However, the mean total dose of alcohol self-injected is low (ca. 0.15 g/kg over 8 h). Given the excesses to which humans are known to abuse alcohol, it is unclear whether fundamental differences exist between rat and man in the perception of positive reinforcement. The IV ethanol self-injection model therefore deserves further study. It is apparent that 5-HT- but not DA-containing neurons can alter ethanol self-injection.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the supply of desipramine generously given them by Merrell Dow Pharmaceuticals (Cincinnati, OH) and fluoxetine hydrochloride (Eli Lilly & Co., Indianapolis, IN). This work was supported in part by a grant from the South Plains Foundation.

REFERENCES

1. Amit, A., Sutherland, E. A.; Gill, K.; Ogren, S. O. Zimelidine: A review of its effects on ethanol consumption. Neurosci. Biobehav. Rev. 8:35–54; 1984.
2. Brown, Z. W.; Amit, Z. The effects of selective catecholamine depletions by 6-hydroxydopamine on ethanol preference in rats. Neurosci. Lett. 5:333–336; 1977.
3. Collins, R. J.; Weeks, J. R.; Cooper, M. M.; Good, A. I.; Russell, R. R. Prediction of abuse liability of drugs using IV self-administered by rats. Psychopharmacology (Berl.) 82:6–13; 1984.
4. Daoust, M.; Moore, N.; Saligaut, C.; Lhuintre, J. P.; Chretien, P.; Boismare, F. Striatal dopamine does not appear involved in the voluntary intake of ethanol by rats. Alcohol 3:15–17; 1986.
5. Daost, M.; Saligaut, C.; Chadelaud, M.; Chretien, P.; Moore, N.; Boismare, F. Attenuation by antidepressant drugs of alcohol intake in rats. Alcohol 1:379–383; 1984.
6. DeNoble, V. J.; Mele, P. C.; Porter, J. H. Intravenous self-administration of pentobarbital and ethanol in rats. Pharmacol. Biochem. Behav. 23:759–763; 1985.
7. Fadda, F. A.; Argiolas, M. R.; Melis, M. R.; Serra, G.; Gessa, G. L. Different effect of acute and chronic ethanol on dopamine metabolism in frontal cortex, caudate nucleus and substantia nigra. Life Sci. 27:979–986, 1980.
8. Froehlich, J. C.; Harts, J.; Lumeng, L.; Li, T.-K. Differences in response to the aversive properties of ethanol in rats selectively for oral ethanol preference. Pharmacol. Biochem. Behav. 31:215–222; 1988.
9. Fuchs, V.; Burbes, E.; Coper, H. The influence of haloperidol and aminooxyacetic acid on etonitazene, alcohol, diazepam and barbital consumption. Drug Alcohol Depend. 14:179–186; 1984.
10. Geis, L. S.; Smith, D. G.; Smith, F. L.; Yu, D. S. L.; Lyness, W. H. Tyrosine influence on amphetamine self-administration and brain catecholamines in the rat. Pharmacol. Biochem. Behav. 25:1027–1033; 1986.
11. Geller, I. Effects of para-chlorophenylalanine and 5-hydroxytryptophan on alcohol intake in the rat. Pharmacol. Biochem. Behav. 1:361–365; 1973.
12. Gunne, L. M. E.; Anggard, E.; Jonsson, L. E. Clinical trials with amphetamine blocking drugs. Psychiatr. Neurol. Neurochim. 75: 225–226; 1972.
13. Leccese, A. P.; Lyness, W. H. Effects of putative 5-hydroxytryptamine receptor active agents on *d*-amphetamine self-administration in controls and rats with 5,7-dihydroxytryptamine median forebrain bundle lesions. Brain Res. 303:153–162; 1984.
14. Linesman, M. A. Effects of dopaminergic agents on alcohol consumption by rats in a limited access paradigm. Psychopharmacology (Berl.) 100:195–200; 1990.
15. Lumeng, L.; Hawkins, T. D.; Li, T.-K. New strains of rats with alcohol preference and nonpreference. In: Thurman, R. G.; Williamson, J. R.; Drott, H. R.; Chance, B., eds. Alcohol and aldehyde metabolizing systems, vol. 3, New York: Academic Press; 1977:537–544.
16. Lyness, W. H. Effect of *L*-tryptophan pretreatment on d-amphetamine self-administration in the rat. Subst. Alcohol Actions/ Misuse 4:305–312; 1983.
17. Lyness, W. H. Simultaneous measurement of dopamine and its metabolites, 5-hydroxytryptamine and 5-hydroxyindoleacetic acid and tryptophan in brain tissue using liquid chromatography with electrochemical detection. Life Sci. 31:1435–1443; 1983.
18. Lyness, W. H.; Friedle, N. M.; Moore, K. E. Destruction of dopaminergic nerve terminals in nucleus accumbens: Effect on *d*-amphetamine self-administration. Pharmacol. Biochem. Behav. 11:553–556; 1979.
19. Lyness, W. H.; Friedle, N. M.; Moore, K. E. Increased self-administration of d-amphetamine after destruction of 5-hydroxytryptaminergic nerves. Pharmacol. Biochem. Behav. 12:937–941; 1980.
20. Max, B. This and that: The war on drugs and the evolution of sulfur. Trends Pharmacol. Sci. 10:483–486; 1989.
21. Murphy, J. M.; McBride, W. J.; Lumeng, L.; Li, T.-K. Monoamine and metabolite levels in CNS regions of the P line of alcohol preferring rats after acute and chronic ethanol treatment. Pharmacol. Biochem. Behav. 19:849–856; 1983.
22. Myers, R. D.; Melchior, C. L. Alcohol drinking in the rat after destruction of serotonergic and catecholaminergic neurons in the brain. Res. Comm. Chem. Pathol. 10:363–378; 1977.
23. Naranjo, C. A.; Sellers, E. M.; Laurin, M. O. Modulation of ethanol intake by serotonin uptake inhibitors. J. Clin. Psychiatry 47(Suppl.):16–22; 1986.
24. Pellegrino, L. J.; Cushman, A. S. A stereotaxic atlas of the rat brain. New York: Appleton-Century Crofts; 1967.
25. Penn, P. E.; McBride, W. J.; Lumeng, L.; Gaff, T. M.; Li, T.-K. Neurochemical and operant behavior studies of a strain of alcohol preferring rats. Pharmacol. Biochem. Behav. 8:475–481; 1978.
26. Roberts, D. C. S.; Corcoran, M. E.; Fibiger, H. C. On the role of ascending catecholamine systems in intravenous self-administration of cocaine. Pharmacol. Biochem. Behav. 6:615–620; 1977.
27. Sinden, J. D.; LeMagnen, J. Parameters of low-dose ethanol intravenous self-administration in the rat. Pharmacol. Biochem. Behav. 16:181–183; 1982.
28. Smith, F. L.; Yu, D. S. L.; Smith, D. G.; Leccese, A. P.; Lyness, W. H. Dietary tryptophan supplements attenuate amphetamine self-administration in the rat. Pharmacol. Biochem. Behav. 25: 849–855; 1986.
29. Smith, J. E.; Schultz, K.; Co, C.; Goeders, N. E.; Dworkin, S. I. Effects of 5,7-dihydroxytryptamine lesions of the nucleus accumbens on rat intravenous morphine self-administration. Pharmacol. Biochem. Behav. 26:607–612; 1987.
30. Socaransky, S. M.; Aragon, C. M. G.; Amit, Z.; Blander, A. Higher correlation of ethanol consumption with brain than liver aldehyde dehydrogenase in three strains of rats. Psychopharmacology (Berl.) 84:250–253; 1984.
31. Weeks, J. R. Experimental morphine addiction: Method for automatic intravenous injection in unrestrained rats. Science 191: 1273–1274; 1976.
32. Weeks, J. R. The pneumatic syringe: A simple apparatus for self-administration of drugs by rats. Pharmacol. Biochem. Behav. 7:559–562; 1977.
33. Wise, R. A. Catecholamine theories of reward: A critical review. Brain Res. 152:215–247; 1978.
34. Wise, R. A. Action of drugs of abuse on brain reward systems. Pharmacol. Biochem. Behav. 13(Suppl. 1):213–223; 1980.
35. Wise, R. A.; Bozarth, M. A psychomotor stimulant theory of addiction. Psychol. Rev. 94:284–287; 1987.
36. Yu, D. S. L.; Smith, F. L.; Smith, D. G.; Lyness, W. H. Fluoxetine-induced attenuation of amphetamine self-administration in rats. Life Sci. 39:1383–1388; 1986.