Pharmacology Biochemistry & Behavior, Vol. 14, pp. 617–623, 1981. Printed in the U.S.A.

The Effects of *d*-Lysergic Acid Diethylamide (LSD), 2,5-Dimethoxy-4-Methylamphetamine (DOM), Pentobarbital and Methaqualone on Punished Responding in Control and 5,7-Dihydroxytryptamine-Treated Rats

R. L. COMMISSARIS[1], W. H. LYNESS[2] AND R. H. RECH

Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824

Received 27 September 1980

COMMISSARIS, R. L., W. H. LYNESS AND R. H. RECH. *The effects of* d-*lysergic acid diethylamide (LSD), 2,5-dimethoxy-4-methylamphetamine (DOM), pentobarbital and methaqualone on punished responding in control and 5,7-dihydroxytryptamine-treated rats.* PHARMAC. BIOCHEM. BEHAV. **14**(5) 617–623, 1981.—The purpose of the present study was to determine the role of central 5-hydroxytryptamine (5-HT) neuronal systems in the effects of *d*-lysergic acid diethylamide (LSD), 2,5-methoxy-4-methylamphetamine (DOM), pentobarbital (PB) and methaqualone (MQ) on punished responding in rats. Water-deprived rats were trained to drink from a tube that was electrified at intervals (variable interval 21 sec; 0.03 mA current intensity), electrification being signalled by a tone. In daily 10-min control sessions, these animals accepted a relatively constant number of shocks; water consumption was also quite stable. At maximally effective doses PB, and to a lesser extent MQ, produced large (400–600 percent of control) increases in punished responding with little decrease in water intake. Higher doses of these agents produced a significant depression of unpunished responding (water intake). The hallucinogens, on the other hand, produced only moderate (125–175 percent of control) increases in the number of shocks received, yet a similar depression of unpunished responding. Selective destruction of 5-HT neurons by intracerebroventricular administration of the neurotoxin 5,7-dihydroxytryptamine *per se* produced little change in the number of shocks received or water consumed in control sessions. This destruction of 5-HT neurons failed to alter the effects of PB or MQ on punished or unpunished responding. The increase in punished responding produced by the hallucinogens, however, was blocked by this destruction of 5-HT neurons. Furthermore, the capacity of the hallucinogens to decrease water intake was significantly potentiated by the neurotoxin pretreatment. These data demonstrate that the effects of the hallucinogens LSD and DOM on conditioned suppression are quite different from those of PB and MQ, and that this difference may be due to the extent of 5-HT involvement in the effects of these agents.

5-Hydroxytryptamine LSD DOM Pentobarbital Methaqualone Conflict behavior

EXPERIMENTAL models for testing anti-anxiety agents have relied largely on paradigms involving punishment-suppressed responding. The experimental design involves schedule-controlled operant responding motivated by an appetitive drive as the background behavior, alternating with periods (cued often by a tone) during which responses are simultaneously rewarded and punished (the latter usually by footshock). Since the subject must accept punishment to attain positive reinforcement during the tone periods, these tests have also been called "conflict" procedures. The benzodiazepines are the most widely prescribed anti-anxiety agents known. Additionally, these agents are most effective in increasing punished responding in these animal models for conditioned suppression used as screens for anti-anxiety drugs [10, 14, 28]. Also effective, both clinically and in the experimental models, are the barbiturates, the forerunners of the benzodiazepines in the treatment of anxiety [17,20]. Although the anti-anxiety properties of methaqualone have been less closely examined, there are reports that this compound is also an effective anti-anxiety agent [11,13].

The precise neuronal basis for the control of punished responding is unknown. It has been suggested that reductions in the activity of brain 5-hydroxytryptamine (5-HT) neurons are causally related to increases in punished responding. This hypothesis is supported by reports that presumptive 5-HT antagonists and synthesis inhibitors are ef-

[1]To whom reprint requests should be addressed.
[2]Present address: Department of Pharmacology and Therapeutics, Texas Tech University, Lubbock, TX 79430.

fective in increasing punished responding [10, 15, 16, 18, 19, 24, 29], although experiments to demonstrate the role of central 5-HT neurons in the anti-conflict effect of the benzodiazepines have not yielded consistent results [6,10]. Tye *et al.* [30] demonstrated that 5,7-dihydroxytryptamine (5,7-DHT) administered into the ventromedial tegmentum of rats blocks the normal acquisition of suppression in a conflict paradigm similar to the classical Geller-Seifter procedure [17]. These authors also presented evidence that the chlordiazepoxide-induced increase in punished responding was attenuated in the 5,7-DHT-treated subjects. The role of 5-HT neurons in the increase in punished responding produced by the barbiturates and methaqualone, however, has not been examined as extensively.

Hallucinogens of both the indolealkylamine (LSD-type) and phenethylamine (mescaline-type) classes produce a number of behavioral effects which are mediated through 5-HT neuronal systems [1–4, 8, 21, 23, 27, 32, 33]. Although these agents are not considered efficacious in the treatment of anxiety, Schoenfeld [26] has reported that LSD and mescaline produce increases in punished responding. These effects have been proposed to relate to the capacity of these agents to inhibit the discharge of brain 5-HT neurons [26].

The purpose of the present study was to determine the effects of pentobarbital (PB), methaqualone (MQ), LSD and the phenethylamine hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) on punished and unpunished responding. The drugs were tested first in control animals and later in the same animals following destruction of 5-HT neurons with the neurotoxin 5,7-dihydroxytryptamine.

METHOD

Subjects

Six female Sprague Dawley rats (200–225 g) were used. These subjects were housed three per cage in a room with a 12-hr day-night cycle (lights on 0700–1900 hr). Since the subjects had been exposed to various barbiturates and alcohol acutely prior to the study (no treatments were administered chronically), a three week drug-free period was observed before the start of the present experiment. During this prior period of drug exposures the subjects had adapted to the "initial treatment phenomenon" peculiar to drug effects on conflict procedures [10]; therefore, predictable drug effects had been achieved. Prior exposures to these agents were not observed to alter subsequent control responding in these subjects.

Behavioral Apparatus

Behavioral training and testing was conducted in the conditioned suppression chamber described by Ford *et al.* [14]. The apparatus is similar to the acute testing chamber used by Vogel *et al.* [31]; it was modified, however, to allow for repeated testing of the subjects. All subjects were tested in daily 10-min sessions between 1400 and 1600 hr. The testing chamber was a rectangular box with Plexiglas sides and a metal floor and top. Protruding from one wall was a metal drinking tube. Seven-second tone periods were produced intermittently (variable interval—21 sec). During the latter 5 sec of these 7-sec periods, contact between the floor and the drinking tube closed a circuit which resulted in the delivery of a 0.03 mA shock to the subject for the duration of the tube contact. Thus, the 10-min sessions were characterized by approximately 8 min of shock-free drinking and approximately 2 min in which tube contact produced a shock. All experimental events were controlled by electromechanical programming circuits and shocks were recorded on electromechanical counters. Shocks were delivered to the mouths of the subjects by a C. J. Applegate (Boulder, CO) Stimulator Model No. 250. Attached to the metal drinking tube was a calibrated (±0.5 ml units) polyethylene drinking tube used to measure the volume of fluid drunk.

Behavioral Procedure

During training water-deprived subjects were placed in the experimental chamber and allowed to drink freely without the shock contingency. After approximately one week of sessions without shock, the shock contingency was incorporated. Initially, the shock inhibited all drinking. After several days, however, all subjects came to drink stable volumes of water (almost entirely in the non-tone periods) and received

TABLE 1

EFFECTS OF INTRAVENTRICULAR 5,7-DHT ADMINISTRATION ON THE CONCENTRATIONS OF 5-HT, DA AND NE IN VARIOUS BRAIN REGIONS

	5-HT		DA		NE	
	Control	5,7-DHT	Control	5,7-DHT	Control	5,7-DHT
Cortex	0.27 ± 0.04	0.04 ± 0.01* (15)	0.30 ± 0.02	0.30 ± 0.01 (100)	0.32 ± 0.02	0.36 ± 0.01 (113)
Hippocampus	0.46 ± 0.03	0.08 ± 0.01* (18)	n.d.	n.d.	0.31 ± 0.01	0.32 ± 0.02 (103)
Hypothalamus	1.14 ± 0.03	0.47 ± 0.09* (39)	n.d.	n.d.	1.61 ± 0.13	1.82 ± 0.11 (113)
Striatum	0.64 ± 0.05	0.06 ± 0.01* (9)	6.29 ± 0.32	6.40 ± 0.36 (102)	n.d.	n.d.

Data are expressed in μg amine/g wet tissue; each value represents the mean ± S.E.M. obtained from six 5,7-DHT-treated (200 μg/10 μl) or six control (no treatment) animals. Numbers in parentheses represent concentrations of amine in 5,7-DHT-treated animals expressed as a percentage of control values.

n.d. = not determined.

*$p < 0.05$, Student's t-test.

TABLE 2

EFFECTS OF 5,7-DHT TREATMENT ON PUNISHED AND UNPUNISHED RESPONDING

	Punished Responding (shocks received)	Unpunished Responding (water intake [ml])
Pre- 5,7-DHT	20 ± 1	13.4 ± 0.3
Post- 5,7-DHT	25 ± 4 (123)	15.1 ± 0.6* (113)

Each value represents the mean ± S.E.M. obtained from six rats before or after administration of 5,7-DHT. Average response parameters for each animal were determined as the mean of the control (no injection) sessions throughout the study. Numbers in parentheses represent percent of control (Pre- 5,7-DHT) values.
*$p<0.05$, Student's t-test.

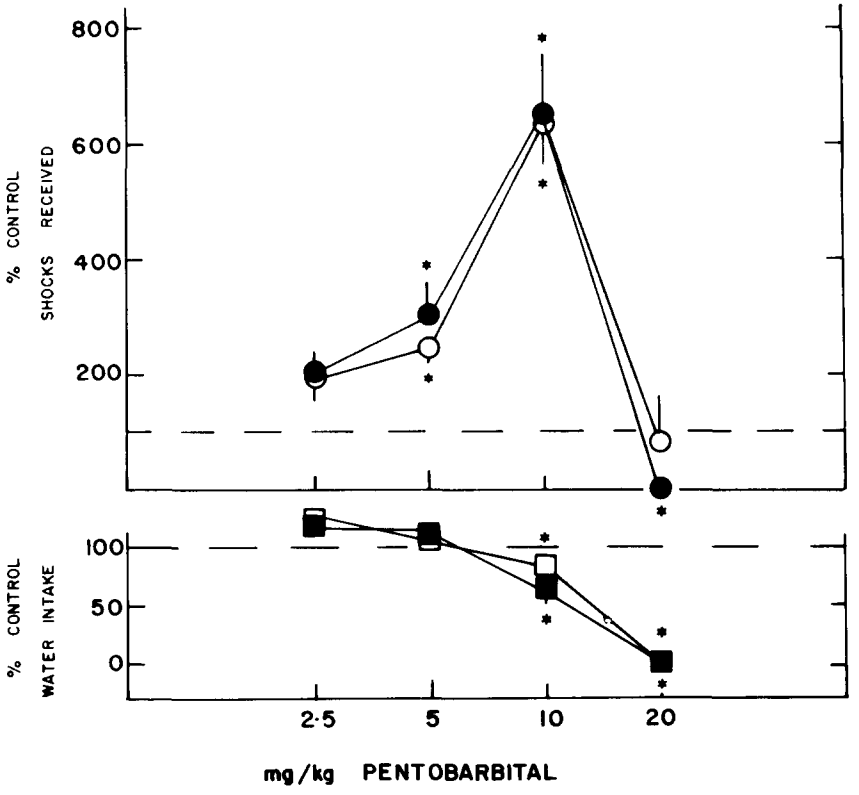

FIG. 1. The effects of pentobarbital on punished and unpunished responding in rats before and after 5,7-DHT treatment. Top panel: percentage of control shocks received (punished responding); bottom panel: percentage of control water intake (unpunished responding). Doses of pentobarbital, dissolved in saline, were administered 10 min prior to testing. Open symbols and vertical bars represent mean ± SEM from six subjects prior to administering the neurotoxin; filled symbols represent the data obtained after intracerebroventricular 5,7-DHT (200 μg/10 μl) treatment. Baseline response parameters (before and after lesioning) are shown in Table 2. Percent of control for each subject was determined by comparing the data on test days to the average of the three days prior to and the three days after the test day (baseline). *Significantly different from baseline values; $p<0.05$ by Student's t-test for paired values. 5,7-DHT administration did not significantly change the response to various doses of pentobarbital.

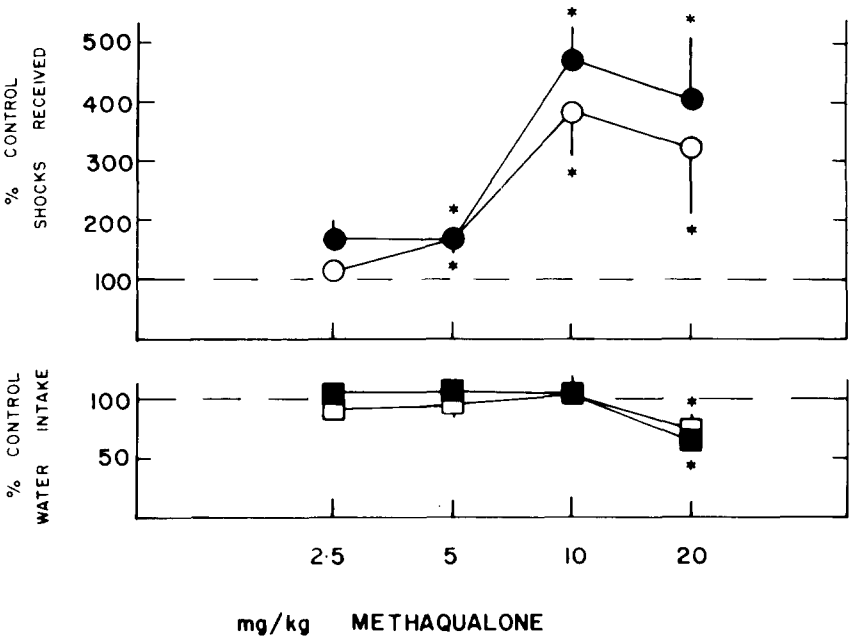

FIG. 2. The effects of methaqualone on punished and unpunished responding in rats before (open symbols) and after (filled symbols) 5,7-DHT treatment. Doses of methaqualone were administered 10 min prior to testing. See Fig. 1 legend for further information. *Significantly different from baseline values; $p<0.05$ by Student's t-test. 5,7-DHT administration did not significantly change the response to various doses of methaqualone.

a consistent number of shocks from day to day. The subjects received no water in addition to the experimental session except on drug testing days in which the subjects failed to drink at least 5–10 ml fluid; these subjects were then allowed free access to water for five min starting at one hr after testing. After responding had become stable for each rat, the effects of various doses of LSD, DOM, PB and MQ were determined in each rat. All drugs were administered IP 10 min prior to the start of the test session. The order of drugs and doses administered was completely randomized for each subject. Drug test days were separated by at least three non-drug sessions to avoid the possibility of tolerance development.

After the effects of these agents were determined, the subjects were anesthetized with equithesin (3 ml/kg) and placed in a stereotaxic apparatus. All subjects received 5,7-dihydroxytryptamine (200 μg/10 μl) intracerebroventricularly. They also received 25 mg/kg desipramine HCl IP 45 min prior to administration of the neurotoxin to protect against the destruction of norepinephrine neurons [5]. The subjects were allowed 3–5 days to recover from surgery before behavioral testing was reinstated. After an additional week of control sessions, water intake and the number of shocks received had stabilized for each rat and the effects of LSD, DOM, PB and MQ were again determined as described above.

Brain Amine Determinations

Following completion of the post-lesion behavioral analyses, the subjects and six untreated animals were sacrificed, their brains were removed, and the concentrations of 5-HT, norepinephrine and dopamine in a number of brain regions were determined by fluorimetric procedures [7,12].

Statistical Analyses

Drug effects were assessed by comparing the data from test days to the average of the three days prior to and three days after the test day (baseline). Student's t-test for paired data were used to evaluate the effects of individual doses of the agents used and to evaluate the effects of 5,7-DHT treatment on baseline conditioned suppression of drinking performance. Dose-response relationships were examined by analysis of variance in a block design. In all statistical evaluations $p<0.05$ was used as the criterion for statistical significance.

Drugs

LSD tartrate and DOM hydrochloride were obtained from the National Institute on Drug Abuse. 5,7-Dihydroxytryptamine creatinine sulfate and pentobarbital sodium were obtained from Sigma Chemical Co. (St. Louis, MO). Desipramine hydrochloride was obtained from Merrell Industries (Cincinnati, OH). Methaqualone free base, obtained from Wm. H. Rorer, Inc. (Fort Washington, PA), was suspended in 0.5% methylcellulose; thus, doses of this agent refer to the free base. All other drugs were administered as the salts dissolved in saline and the doses listed below are calculated on the basis of the salt forms.

RESULTS

Pretreatment with 5,7-DHT significantly decreased the concentration of 5-HT in all brain areas examined, when these subjects were compared with untreated control rats (Table 1). The concentrations of dopamine and/or norepinephrine in these areas were not significantly altered. These

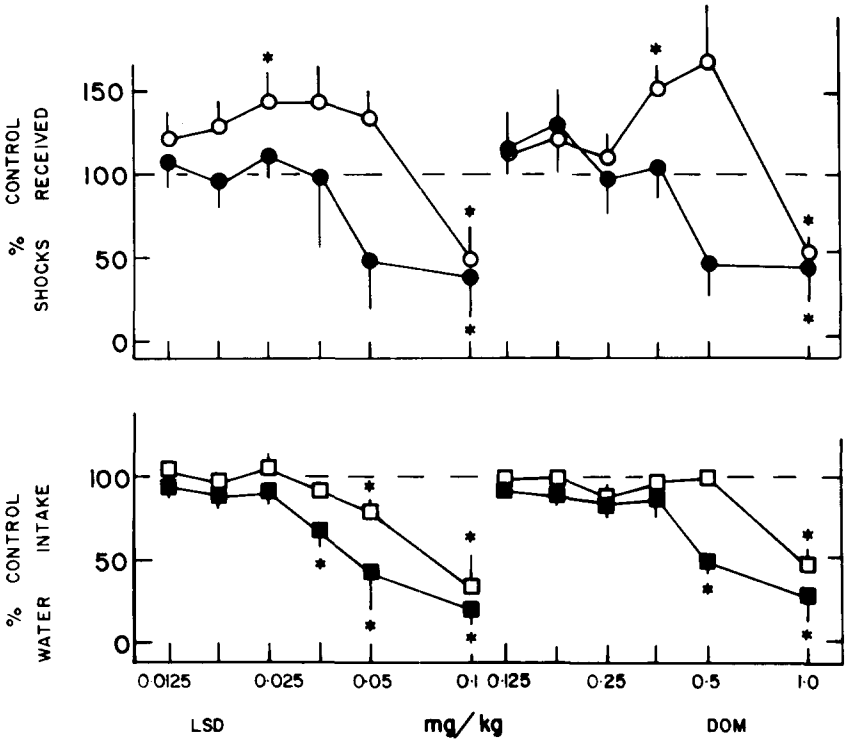

FIG. 3. The effects of LSD and DOM on punished and unpunished responding in rats before (open symbols) and after (filled symbols) 5,7-DHT treatment. The effects of various doses of LSD (12.5–100 μg/kg) are represented by the symbols on the left side of the figure; the effects of DOM (0.125–1.0 mg/kg) are represented by symbols on the right side of the figure. Both agents were dissolved in saline and administered 10 min prior to the start of the session. See Fig. 1 legend for further imformation. *Significantly different from baseline values, $p<0.05$ by Student's t-test for paired values. 5,7-DHT significantly attenuated the effects of both agents to increase number of shocks received (top panel); 5,7-DHT treatment significantly potentiated the capacity of both agents to decrease water intake.

amine concentrations in untreated rats are similar to those which we have reported previously following intraventricular administration of the neurotoxin vehicle [9]. The disruption of 5-HT neuronal activity did not significantly alter the number of shocks received in post-lesion control sessions in this conflict procedure (Table 2). Water intake, however, was significantly greater following 5,7-DHT treatment. This effect was probably not due to the 5,7-DHT treatment *per se* since we have observed that a similar group of six untreated subjects showed an increase from 13.3±0.3 to 14.9±0.7 ml water consumed over the course of a 6 month period (the time elapsed during the present study).

Before 5,7-DHT treatment PB produced a dose-dependent increase in the number of shocks received (relative to baseline) between 2.5 and 10 mg/kg, and a dose-dependent decrease in water intake between 10 and 20 mg/kg (Fig. 1). A decrease in punished responding at 20 mg/kg was correlated with the highly sedative effects of this dose. Maximal anticonflict activity for PB was observed at the 10.0 mg/kg dose, at which dose punished responding was increased to greater than 600 percent of control. Water intake was slightly depressed by this dose. Treatment with 5,7-DHT did not significantly alter the effects of PB on either punished or unpunished responding.

In control animals, MQ produced a dose-dependent increase in punished responding between 2.5 and 10.0 mg/kg (Fig. 2). Maximal anti-conflict activity of this agent was also obtained at the 10.0 mg/kg dose, which increased punished responding to almost 400 percent of control. Water intake was not depressed by this dose of MQ. A significant decrease in water intake was observed at the 20.0 mg/kg dose in control animals, however. Treatment with 5,7-DHT did not alter the effects of MQ on either punished or unpunished responding, although there was a tendency for MQ to produce a greater increase in punished responding after 5,7-DHT treatment.

In control animals both LSD and DOM produced a dose-dependent decrease in water intake (Fig. 3). Many doses of these agents produced a tendency for a modest increase in punished responding, but this effect was found to be significant only with the 25 μg/kg LSD and 0.35 mg/kg DOM doses. A trend for maximal anticonflict activity was observed with the 35 μg/kg LSD and 0.50 mg/kg DOM doses, at which doses mean values for punished responding were increased to 142 and 175 percent of control, respectively. Pretreatment with 5,7-DHT attenuated the effects of both LSD and DOM to increase punished responding over the entire range of doses. Furthermore, 5,7-DHT treatment potentiated the dose-dependent depression of water intake observed after both hallucinogens.

DISCUSSION

Destruction of 5-HT neurons with 5,7-DHT failed to alter punished responding in these animals. These data suggest that the activity of 5-HT neurons is not important in maintaining basal levels of punished responding in this procedure for conditioned suppression of drinking. This finding is in contrast to reports that decreasing 5-HT activity by treatment with 5,7-DHT, 5,6-dihydroxytryptamine, putative 5-HT antagonists and the 5-HT synthesis inhibitor *p*-chlorophenylalanine produce an increase in punished responding in Geller-Seifter-type paradigms for food reinforcement [6, 15, 16, 19, 24, 28, 29] or block the acquisition of suppression by punishment [30]. This discrepancy could be due to the differences in the two paradigms, including the difference in the reinforcers used, since it has been reported that decreases in 5-HT neuronal activity result in increased motivation for food reinforcement [25]. Water intake during control sessions increased following 5,7-DHT treatment. Since control animals also tend to show similar increases in the volume of water drunk per session during repeated daily testing over the same time period (unpublished data), this effect is probably not due to the 5,7-DHT treatment but rather to the extended testing.

PB, and to a lesser extent MQ, produced large and significant increases in punished responding, and at higher doses both drugs decreased unpunished responding. The efficacy of PB reported here is in agreement with previous reports [17] on this agent. The anti-conflict actions of MQ described above confirm an earlier study in rats [22] and are consistent with the clinical anti-anxiety effects of this agent [11,13]. The effects of PB and MQ were not altered by 5,7-DHT treatment. Therefore, it appears that the anti-conflict activity of these agents is not associated with an alteration in the activity of 5-HT pathways.

The increase in punished responding produced by LSD and DOM is rather tenuous, perhaps reflecting the disturbance of many cognitive functions, some of which may tend to increase punished responding while others tend to impair behavioral responses more generally. The anticonflict activity of these agents does appear to involve brain 5-HT pathways, since 5,7-DHT treatment blocks this effect. The high-dose disruptions of water intake by LSD and DOM are enhanced in 5,7-DHT subjects. This effect is in agreement with previous reports in which it has been shown that 5,7-DHT treatment potentiates the disruptive effects of hallucinogens on fixed ratio-40 operant responding [4,8].

The effects of benzodiazepines to increase punished responding have been proposed as being mediated through an interference with 5-HT activity to forebrain areas [10, 20, 28]. However, Tye *et al.* [30] indicated that the chlordiazepoxide-induced increase in punished responding appeared to be attenuated in 5,7-DHT-lesioned rats. Furthermore, Kilts [22] examined interactions of benzodiazepines with other treatments affecting central 5-HT activity in the conditioned suppression of drinking paradigm used here; he demonstrated that several treatments known to enhance brain 5-HT activity actually potentiated the anti-conflict effects of diazepam. Thus, the relationship between the increase in punished responding by benzodiazepines and forebrain 5-HT neuronal activity appears to be poorly understood at this time.

The anti-conflict activity of LSD and DOM is weak at best. Furthermore, destruction of 5-HT neurons does not alter the punished responding in control sessions. Therefore, the influence of 5-HT neuronal activity on this particular behavior seems to be slight indeed. Moreover, destruction of brain 5-HT neurons did not alter the anti-conflict effects of MQ or PB. These data suggest that 5-HT neurons are involved in the increase in punished responding produced by some agents, but not others.

ACKNOWLEDGEMENTS

The authors acknowledge the excellent technical assistance of David R. Semeyn and Barbara Z. Stetler. This work was supported by grant No. DA-01836 from the National Institute on Drug Abuse. R. Commissaris is a predoctoral student supported by USPHS Training Grant GM-07392.

REFERENCES

1. Aghajanian, G. K., H. J. Haigler and J. L. Bennett. Amine receptors in CNS. III. 5-Hydroxytryptamine in brain. In: *Handbook of Psychopharmacology*, Vol. 6, edited by L. L. Iversen, S. D. Iversen and S. H. Snyder. New York: Plenum Press, 1975, pp. 63–69.
2. Andén, N. E., H. Corrodi, K. Fuxe and T. Hökfelt. Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide. *Br. J. Pharmac.* **34:** 1–7, 1968.
3. Andén, N. E., H. Corrodi, K. Fuxe and J. L. Meek. Hallucinogenic phenethylamines: interactions with serotonin turnover and receptors. *Eur. J. Pharmac.* **25:** 176–184, 1974.
4. Appel, J. B., J. A. Joseph, E. Utsey, L. L. Hernandez and W. O. Boggan. Sensitivity to psychoactive drugs and the serotonergic neuronal system. *Communs Psychopharmac.* **1:** 541–551, 1977.
5. Björklund, A., H. G. Baumgarten and A. Rensch. 5,7-Dihydroxytryptamine: improvement of its selectivity for serotonin neurons in the CNS by pretreatment with desipramine. *J. Neurochem.* **24:** 833–835, 1975.
6. Blakely, T. A. and L. F. Parker. The effects of parachlorophenylalanine on experimentally induced conflict behavior. *Pharmac. Biochem. Behav.* **1:** 609–613, 1973.
7. Chang, C. C. A sensitive method for spectrofluorimetric assay of catecholamines. *Int. J. Neuropharm.* **3:** 643–649, 1964.
8. Commissaris, R. L., W. H. Lyness, R. H. Rech and K. E. Moore. Central aminergic neuronal systems and the behavioral effects of hallucinogens. *Soc. Neurosci. Abstr.* **5:** 644, 1979.
9. Commissaris, R. L., W. H. Lyness, J. J. Cordon, K. E. Moore and R. H. Rech. The effects of *d*-lysergic acid diethylamide (LSD), 2,5-dimethoxy-4-methylamphetamine (DOM) and *d*-amphetamine on operant responding in control and 6-hydroxytryptamine-treated rats. *Pharmac. Biochem. Behav.* **13:** 621–626, 1980.
10. Cook, L. and J. Sepinwall. Behavioral analysis of the effects and mechanism of action of benzodiazepines. In: *Mechanism of Action of Benzodiazepines*, edited by E. Costa and P. Greengard. New York: Raven Press, 1975, pp. 1–28.
11. Cromwell, H. A. Methaqualone—a sedative or minor tranquilizer for geriatric patients. *J. Am. Geriat. Soc.* **16:** 814–817, 1968.
12. Curzon, G. and A. R. Green. Rapid method for the determination of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in small regions of rat brain. *Br. J. Pharmac.* **39:** 653–655, 1970.
13. Duchastel, Y. Methaqualone; a synthetic nonbarbiturate hypnotic: a "double blind" clinical evaluation of 100 cases. *Can. med. Ass. J.* **86:** 586–587, 1962.

14. Ford, R. D., R. H. Rech, R. L. Commissaris and L. Mayer. Effects of acute and chronic interactions of diazepam and *d*-amphetamine on punished and unpunished behavior of rats. *Psychopharmacology* **65:** 197–204, 1979.
15. Geller, I. and K. Blum. The effects of 5-HTP on para-chlorophenylalanine (*p*-CPA) attenuation of "conflict" behavior. *Eur. J. Pharmac.* **9:** 319–324, 1970.
16. Geller, I., R. J. Hartmann and D. J. Croy. Attenuation of conflict behavior with cinanserin, a serotonin antagonist: Reversal of the effect with 5-hydroxytryptophan and α-methyltryptamine. *Res. Communs chem. pathol. Pharmac.* **7:** 165–174, 1974.
17. Geller, I. and J. Seifter. The effect of meprobamate, barbiturates, *d*-amphetamine and promazine on experimentally-induced conflict in the rat. *Psychopharmacologia* **1:** 482–491, 1960.
18. Graeff, F. G. and R. I. Schoenfeld. Tryptaminergic mechanisms in punished and nonpunished behavior. *J. Pharmac. exp. Ther.* **173:** 277–283, 1970.
19. Graeff, F. G. Tryptamine antagonists and punished behavior. *J. Pharmac. exp. Ther.* **189:** 344–350, 1974.
20. Haefely, W. E. Behavioral and neuropharmacological aspects of drugs used in anxiety and related states. In: *Psychopharmacology: A Generation of Progress*, edited by M. A. Lipton, A. DiMascio and K. F. Killam. New York: Raven Press, 1978, pp. 1359–1374.
21. Haigler, H. J. and G. K. Aghajanian. Mescaline and LSD: Direct and indirect effects on serotonin-containing neurons in brain. *Eur. J. Pharmac.* **21:** 53–60, 1973.
22. Kilts, C. D. Relationship of amygdaloid 5-hydroxytryptamine-containing neurons to anticonflict effects of benzodiazepines in the rat. Doctoral Dissertation, Michigan State University, East Lansing, MI, 1980.
23. Kuhn, D. M., F. J. White and J. B. Appel. The discriminative stimulus properties of LSD: Mechanisms of action. *Neuropharmacology* **17:** 257–263, 1978.
24. Robichaud, R. C. and K. L. Sledge. The effects of p-chlorophenylalanine on experimentally induced conflict in the rat. *Life Sci.* **8:** 965–969, 1969.
25. Samanin, R., C. Bendotti, G. Candelaresi and S. Garattini. Specificity of serotonergic involvement in the decrease of food intake induced by quipazine in the rat. *Life Sci.* **21:** 1259–1266, 1978.
26. Schoenfeld, R. I. Lysergic acid diethylamide- and mescaline-induced attenuation of the effect of punishment in the rat. *Science* **192:** 801–803, 1976.
27. Sloviter, R., E. Drust, B. Dammiano and J. Connor. A common mechanism for lysergic acid, indole alkylamine and phenethylamine hallucinogens: serotonergic mediation of behavioral effects in rats. *J. Pharmac. exp. Ther.* **214:** 231–238, 1980.
28. Stein, L., C. D. Wise and B. D. Berger. Antianxiety action of benzodiazepines: Decrease in activity of serotonin neurons in the punishment system. In: *The Benzodiazepines*, edited by S. Garattini, E. Mussini and L. O. Randall. New York: Raven Press, 1973, pp. 299–326.
29. Stein, L., C. D. Wise and J. D. Belluzzi. Effect of benzodiazepines on central serotonergic mechanisms. In: *Mechanisms of Action of Benzodiazepines*, edited by E. Costa and P. Greengard. New York: Raven Press, 1975, pp. 29–44.
30. Tye, N. C., B. J. Everitt and S. D. Iversen. 5-Hydroxytryptamine and punishment. *Nature Lond.* **268:** 741–743, 1977.
31. Vogel, J. R., B. Beer and D. E. Clody. A simple and reliable conflict procedure for testing anti-anxiety agents. *Psychopharmacologia* **21:** 1–7, 1971.
32. Winter, J. C. Stimulus properties of phenethylamine hallucinogens and LSD: The role of 5-hydroxytryptamine. *J. Pharmac. exp. Ther.* **204:** 416–423, 1978.
33. Winter, J. C. Quipazine-induced stimulus control in the rat. *Psychopharmacology* **60:** 265–269, 1979.