Pharmacology Biochemistry & Behavior, Vol. 18, pp. 41–45, 1983. Printed in the U.S.A.

Cyclazocine Disruption of Operant Behavior is Antagonized by Naloxone and Metergoline[1]

JUDITH W. HENCK, DAVID J. MOKLER, RANDALL L. COMMISSARIS[2] AND RICHARD H. RECH

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

Received 28 July 1982

HENCK, J. W., D. J. MOKLER, R. L. COMMISSARIS AND R. H. RECH. *Cyclazocine disruption of operant behavior is antagonized by naloxone and metergoline.* PHARMACOL BIOCHEM BEHAV **18**(1) 41–45, 1983.—Male Sprague-Dawley rats were trained to press a lever on a fixed ratio-40 (FR-40) schedule for food reinforcement. Doses ranging from 0.5 to 16 mg/kg of the mixed narcotic agonist-antagonist cyclazocine (30-min pretreatment) resulted in a dose-dependent decrease in the number of reinforcements obtained and a reciprocal increase in "pausing" (IRT's greater than 10 sec). A 5-min pretreatment with 4 mg/kg of the narcotic antagonist naloxone attenuated the cyclazocine disruption. The 5-HT antagonist metergoline (1 mg/kg; 180-min pretreatment) also blocked cyclazocine effects to approximately the same degree as did naloxone. However, the shift of the dose response pattern of cyclazocine was not parallel for either antagonist. A greater degree of attenuation of the cyclazocine effects was observed when naloxone (4 mg/kg) and metergoline (0.1 mg/kg) were given together, indicating that cyclazocine disruption may be antagonized by either a narcotic antagonist or a 5-HT antagonist, and that these antagonists may operate synergistically. Thus, the behavioral effects of cyclazocine may relate to both opioid and serotonergic components.

Cyclazocine Naloxone Metergoline Rat Operant behavior

CYCLAZOCINE is one of a series of N-substituted benzomorphan derivatives which are mixed narcotic agonist-antagonists. Small doses of cyclazocine in humans produce subjective changes (e.g., analgesia, miosis, respiratory depression, constipation) resembling those seen with small to moderate doses of morphine, while larger doses produce subjective and objective changes unlike morphine (e.g., irritability, uncontrollable thoughts, delusions, hallucinations) [17]. The physical dependence produced by cyclazocine is qualitatively different from that produced by narcotic analgesics [16]. In certain respects cyclazocine resembles either barbiturates [16] or tricyclic antidepressants [10]. It was concluded from a discriminative stimulus study that cyclazocine effects are the result of two components: (1) a narcotic component antagonized by naltrexone but not mediated through morphine receptors and (2) a non-narcotic component not antagonized by naltrexone but mimicked by the non-opioids phencyclidine and ketamine [24]. This premise was supported by a subsequent study which showed no generalization between morphine and cyclazocine in a discriminative stimulus procedure [27].

The present study examined the effects of cyclazocine on a fixed ratio-40 (FR-40) schedule of responding for food reinforcement and assessed the capacity of the narcotic antagonist naloxone to attenuate the anticipated operant behavioral deficit [1,12]. Clinically, cyclazocine behaves to some degree as an hallucinogen, and hallucinogens such as *d*-lysergic acid diethylamide (LSD), N,N-dimethyltryptamine, 2,5-dimethoxy-4-methylamphetamine, and mescaline appear to alter the pattern of FR-40 operant behavior by acting as agonists at 5-HT receptors [4–8, 19]. In these studies the degree of "pausing" (lapses in response longer than 10 sec) was quantified to show (together with reinforcements) a pattern of change that was somewhat specific for hallucinogenic drugs, supporting earlier studies by several investigators (see Tilson and Sparber [25]). In order to determine if cyclazocine affects this operant behavior in a similar manner (via 5-HT receptors), interactions with the putative 5-HT antagonist metergoline were tested. To assess interrelationships of the cyclazocine effects on opioid and 5-HT receptors, combinations of naloxone and metergoline were also examined for antagonism of the dose-response pattern of cyclazocine.

METHOD

Subjects

Male Sprague-Dawley rats (Spartan Research Animals, Inc., Haslett, MI), approximately ten weeks of age at the beginning of the experiment, were acclimated to the laboratory environment for at least two weeks prior to testing and were housed individually in a room with a 12-hour light-dark

[1]Supported in part by NIDA Grant DA-01836, NIGMS Training Grant 07392, and Michigan State University BRS Grant 71-0911.
[2]Present address: Department of Psychiatry, Yale University School of Medicine, 34 Park Street, New Haven, CT 06508, USA.

TABLE 1

EFFECTS OF CYCLAZOCINE ALONE AND IN COMBINATION WITH NALOXONE AND/OR METERGOLINE ON REINFORCEMENTS AND PAUSE INTERVALS

		Cyclazocine Dose (mg/kg)						
	Change in:	0.5	1	1.4	2	4	8	16
Cyclazocine Alone	Reinforcements	−11.2±6.1	−28.5± 8.5	−53.6±13.1	−60.5± 6.6	− 89.9±11.9	−113.8±13.4	−139.6±11.8
	Pause Intervals	− 1.8±6.6	16.9±11.7	39.0±14.7	64.5±20.4	106.0±17.2	133.3±15.1	180.4±12.5
+4 mg/kg Naloxone	Reinforcements	5.4±7.3	1.2± 4.2	− 2.4± 5.8*	−39.9±14.1	− 52.4±11.5*	− 86.2±17.1	−132.0±10.0
	Pause Intervals	− 3.9±1.1	− 4.0± 4.7	− 8.7± 4.9*	22.0±12.2*	31.7±20.7*	98.5±19.8	172.0± 9.6
+1 mg/kg Metergoline	Reinforcements	−19.3±6.6	−46.6± 4.1†	−41.8±17.4†	−35.6±13.8	− 66.2±22.1*	− 82.6±22.4	−155.4±15.5
	Pause Intervals	− 1.3±5.9	14.1± 6.2	14.2±15.7	29.3± 9.9*	47.0±16.0*	102.3±23.0	179.8± 9.5
+0.1 mg/kg Metergoline	Reinforcements	−11.2±5.4	− 5.4± 8.2‡	− 9.3±11.8*‡	−23.2±14.2*	− 34.8±11.2*	− 47.4± 9.9*†‡	−133.6±13.9
+4 mg/kg Naloxone	Pause Intervals	− 8.3±3.3	−20.7± 8.5	−11.6± 4.7*	− 4.1± 6.8*	− 0.5±12.8*	19.6± 9.2*†‡	142.7±21.0

Control reinforcements ranged from 99.6±6.5 to 148.9±13.8; control pause interval scores ranged from 23.1±4.8 to 38.7±4.9.
*Significantly different from cyclazocine alone by ANOVA and LSD test ($p<0.05$).
†Significantly different from cyclazocine plus naloxone by ANOVA and LSD test ($p<0.05$).
‡Significantly different from cyclazocine plus metergoline by ANOVA and LSD test ($p<0.05$).

cycle. The animals had no previous drug treatment prior to the start of the experiment and were maintained at 70–80% of their free-feeding weight with laboratory chow (Wayne Lab-Blox, Chicago, IL). Tap water was available ad lib during nontesting periods.

Test Materials

Cyclazocine base (a gift from Sterling-Winthrop Research Institute, Rensselaer, NY) and metergoline (a gift from Farmitalia Carlo Erba, Milan, Italy) were suspended in 0.5% methyl cellulose. Naloxone HCl (Endo Labs, Garden City, NY) was dissolved in distilled water. All drug doses were injected intraperitoneally in a volume of 1 ml/kg.

Apparatus

Each rat was trained and tested for the duration of the experiment in a standard operant chamber (LVE 143-20-215) located in a sound-attenuated box. Each chamber was equipped with a food pellet dispenser and a single lever requiring a force of 10–15 g to activate. All experimental events were controlled by electromechanical programming and the number of reinforcements and periods of non-responding ("pausing") for each rat during daily 40-min sessions were monitored on electromagnetic counters. To quantify the period of non-responding (10-sec intervals without a response) a pause-interval counter [3] was incorporated into the program.

Behavioral Procedure

Each subject was first trained to a continuous reinforcement schedule for food (45 mg Bio-Serv pellets; Bio-Serv, Inc., Frenchtown, NJ) and run at the same time of day in the same cage Monday through Saturday. The schedule was increased gradually on a fixed ratio up to FR-40. After FR-40 responding had stabilized (at least three weeks), testing was initiated. Each rat received 0.5, 1, 1.4, 2, 4, 8 or 16 mg/kg cyclazocine in a completely random order. Each rat then received 4 mg/kg naloxone or 1 mg/kg metergoline in conjunction with all doses of cyclazocine, again in a random order. In the final phase of the experiment all rats received a combination of 4 mg/kg naloxone and 0.1 mg/kg metergoline with each cyclazocine dose. Cyclazocine was administered 30 min prior to, naloxone 5 min prior to, and metergoline 180 min prior to the test session. At least two drug-free days were provided prior to a drug-test day to avoid the possibility of tolerance development.

Statistical Analyses

Data from control days immediately preceding a drug-test day were compared to data obtained on the test day. The effects of individual doses of drugs on reinforcements and pause intervals were evaluated by analysis of variance. Dose-response relationships of cyclazocine and cyclazocine/antagonist combinations were examined by multifactorial analysis of variance and the least significant difference test [23]. The level of significance for all cases was $p<0.05$. ED_{50} values for cyclazocine effects on reinforcements and pause intervals were calculated by probit analysis.

RESULTS

Control FR-40 responding is characterized by a rapid, constant rate of responding with brief pauses (usually following the delivery of a food pellet reinforcement) throughout the operant session. Table 1 lists the control means for reinforcements ±S.E.M. and pause intervals ±S.E.M. as well as changes for all drug combinations tested, and indicates significant differences between scores on control vs drug-test days. Figure 1A depicts the pattern of reinforcements, as a percent of control, resulting from each drug treatment, while Fig. 1B shows changes in pause intervals over baseline values. Significant differences between a drug treatment and baseline control as well as between various drug treatments are illustrated in the figure by half-filled or filled symbols (see Fig. 1 legend).

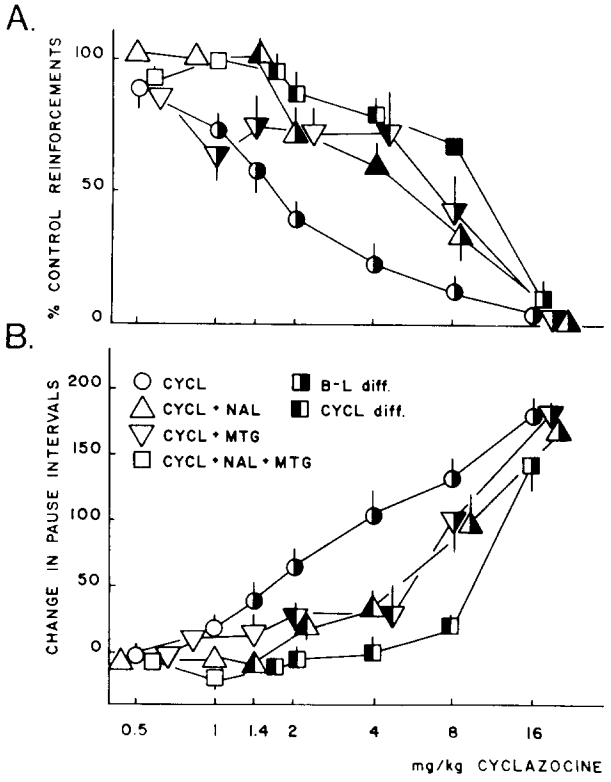

FIG. 1. Naloxone and metergoline antagonism of the effects of cyclazocine. The decrease in reinforcements (A) and change in pause intervals (B) from control values are plotted for various doses of cyclazocine (injected 30 min prior to session; circles), cyclazocine plus naloxone (4 mg/kg, 5 min prior to session; upright triangles), cyclazocine plus metergoline (1 mg/kg, 180 min prior to session; inverse triangles), and cyclazocine plus naloxone and metergoline (4 mg/kg and 0.1 mg/kg, respectively; squares). Reinforcements are presented as percentage of control for clarity, but statistical analysis was conducted on the raw data. Symbols shaded on the right half represent values significantly different ($p<0.05$) from the average of baseline values of the two days prior to the test day. Symbols shaded on the left represent values significantly different ($p<0.05$) from those obtained for the dose of cyclazocine alone. Each symbol and vertical bar represents the mean±S.E.M. for eight to twelve subjects; where no vertical line appears the S.E.M. is less than the radius of the symbol.

Cyclazocine alone resulted in a dose-related decrease in reinforcements (ED_{50}=1.79 mg/kg; 1.12–2.69 mg/kg, 95% confidence interval) and a dose-related increase in IRT's greater than 10 sec ("pausing"; ED_{50}=4.07 mg/kg; 2.31–9.04 mg/kg, 95% confidence interval), relative to control scores for reinforcements or pausing. A dose of 4 mg/kg naloxone alone produced no change in FR-40 responding. However, naloxone caused a statistically significant antagonism of the disruptive effects of 1.4, 2 (pausing only), and 4 mg/kg cyclazocine. Doses of 0.1 or 1 mg/kg metergoline alone had no significant effect on FR-40 operant responding in this study. Metergoline pretreatment caused a statistically significant antagonism of the disruptive effects of 2 (pausing) and 4 mg/kg (reinforcements and pausing) cyclazocine. In addition, the combination of 1 mg/kg metergoline and 1 or 1.4 mg/kg cyclazocine was significantly different from the combination of 4 mg/kg naloxone and 1 or 1.4 mg/kg cyclazocine with regard to reinforcements only.

Various doses of cyclazocine were also combined with 4 mg/kg naloxone and 0.1 mg/kg metergoline. We considered that the results using 0.1 mg/kg metergoline could be compared statistically with results using 1 mg/kg metergoline since these doses were shown in other animals to produce the same degree of antagonism of cyclazocine effects (data not shown). A dose of 0.1 mg/kg metergoline was used in this portion of the study to reduce possible complicating interactions between the antagonists relating to nonspecific neurotoxicity. The combination of naloxone and metergoline caused antagonism of the disruptive effects of 1.4 to 8 mg/kg cyclazocine. The combination of the two antagonists plus 8 mg/kg cyclazocine was significantly different from metergoline plus 8 mg/kg cyclazocine and naloxone plus 8 mg/kg cyclazocine for both reinforcements and pauses. Combinations of metergoline, naloxone, and either 1 or 1.4 mg/kg cyclazocine were significantly different in reinforcements obtained from metergoline plus 1 or 1.4 mg/kg cyclazocine.

DISCUSSION

Cyclazocine, administered alone, produced, in general, a dose-dependent decrease in reinforcements obtained and a reciprocal increase in pause intervals. However, a lower dose of cyclazocine (1 mg/kg) was more effective in slowing the rate of lever pressing than in inducing pausing (1.4 mg/kg), and ED_{50}'s for the two measures differed considerably (1.79 mg/kg vs 4.07 mg/kg, respectively). Cyclazocine has been shown to decrease reinforcements obtained in other operant studies over a range of 0.1 to 10 mg/kg [1,12]. Therefore, the operant schedule and/or subjects used here were not quite as susceptible to the rate-decreasing effects of cyclazocine as in some previous reports, although the decrements occurred over the same approximate dose range.

In human subjects many of the effects of cyclazocine resemble those of morphine, as expected since both agents interact with opiate receptors. Naloxone antagonized the pupillary, respiratory depressant, behavioral and psychotomimetic effects of cyclazocine at a dose fifty times greater than that required to antagonize morphine [15]. Naloxone also antagonized the effects of cyclazocine in the discrete trial shock-titration procedure in monkeys [9] and in the continuous avoidance and locomotor activity paradigms in the rat [14]. Thus, it is not surprising that naloxone antagonized the rate-decreasing effects of cyclazocine and was at least as effective in reversing the pausing induced by cyclazocine in the present study. But in the case of both measures larger doses of cyclazocine overcame the antagonism by naloxone, so that the shifts in the log-dose patterns of cyclazocine were not parallel.

The fact that naloxone blocks doses of morphine ranging from 1–30 mg/kg [1,12] but not higher doses of cyclazocine, as well as requiring a much larger dose range to antagonize cyclazocine [15], supports the concept that these two agonistic effects do not involve the same spectrum of neuronal receptors. This idea is reinforced by discriminative stimulus studies in which cyclazocine did not generalize to morphine, pentazocine, LSD, mescaline, or *d*-amphetamine, but did generalize to nalorphine, ketamine and phencyclidine [20, 24, 27]. In the drug discrimination paradigm cyclazocine effects were blocked by the narcotic antagonists naloxone or

naltrexone. Thus, cyclazocine effects may involve two components: a narcotic factor and a non-narcotic influence. It has been postulated that cyclazocine is a mu opiate receptor antagonist and a mixed kappa and sigma receptor agonist [11]. Receptor binding studies also support the thesis that cyclazocine interacts with three distinct receptor sites [28].

Cyclazocine showed a dose-related increase in "pausing" with a reciprocal decrease in reinforcements: a type of response reported previously in the FR-40 paradigm for hallucinogens of the phenethylamine and indolealkylamine classes [3–5, 7, 21], but not for non-hallucinogenic drugs such as *d*-amphetamine, phenobarbital and chlorpromazine. The effect of hallucinogens in this behavior appears to be mediated by agonistic effects at serotonergic neurons [2, 5–7, 25]. Other operant schedules have also distinguished between the effects of hallucinogens and stimulants [26]. Selective destruction of brain serotonergic neurons potentiated the behaviorally disruptive effects of hallucinogens of both classes [5], and 5-HT antagonists (metergoline, BC-105) blocked the hallucinogenic actions [6, 8, 19]. Furthermore, naloxone (1–5.6 mg/kg) potentiated the effects of hallucinogens on operant behavior [4,21], shifting the dose-response curves in a non-parallel fashion, and a low dose of morphine antagonized the disruption of fixed-ratio responding by N,N-dimethyltryptamine [21]. Therefore, endogenous enkephalinergic activity at mu receptors provoked by the stress of hallucinogenic drug actions may modulate to some degree the disruptive behavioral effects of these hallucinogens. Naloxone may potentiate the disruption produced by hallucinogens by interfering with this mu receptor modulation. Yet, naloxone may antagonize the FR-40 disruption caused by cyclazocine by blocking access of this latter drug to sigma receptors. This proposal is being tested more specifically in our laboratories.

The altered FR-40 pattern by the lowest doses of cyclazocine may be exerted via opioid receptors, since naloxone but not metergoline reversed the effects at this lower dose range (Fig. 1). However, somewhat larger doses of cyclazocine appear to act via a serotonergic element, since at this dose range metergoline pretreatment was antagonistic. That a small dose of metergoline combined with naloxone potentiates the antagonism to a prominent degree also could mean that the two antagonists attenuate the actions of cyclazocine by different mechanisms. Since the larger doses of cyclazocine tested (8 and 16 mg/kg) overcame the antagonism of naloxone or metergoline, and 16 mg/kg overcame the combined effects of the antagonists, neither mechanism of antagonism may fit a simple competitive model. Alternatively, the antagonism may be overcome by an unrelated disruptive influence of cyclazocine. The more extensive study of other dose combinations of the three agents may resolve this issue. Previous findings showed that metergoline did cause a parallel shift to the right of the dose-response curves of indole and phenethylamine hallucinogens for disruption of FR-40 responding, as well as for the effects of the 5-HT agonist quipazine [6,8], indicating that these interactions probably relate to a simpler competition involving 5-HT sites. In a preliminary communication [13] we have indicated that there are also complex interactions between quipazine and cyclazocine in FR-40 operant behavior. Some dose combinations resulted in antagonism of the disrupted behavior observed with a single drug (reversible by metergoline), while other dose combinations caused potentiation of the disruption (reversible by naloxone). This complements a study by Samanin *et al.* [22] that quipazine manifests some opioid-like actions that are antagonized by metergoline. Minnema *et al.* [18] demonstrated that quipazine's antinociceptive actions were antagonized either by the opioid antagonist naltrexone or the 5-HT antagonist BC-105, another indication that quipazine's central effects may involve both opioid and serotonergic systems. More study is obviously required to elucidate the complex interactions of cyclazocine with brain opioid and 5-HT mechanisms.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation to Michelle Imlay, Martin Rewa and Barbara Stetler for technical help, to Diane Hummel for help in preparation of the manuscript, and to Dr. Gregory Fink for advice on the statistical aspects of the study.

REFERENCES

1. Adam-Carriere, D., Z. Merali and R. Stretch. Effects of morphine, naloxone, *d,l*-cyclazocine, and *d*-amphetamine on behavior controlled by a schedule of interresponse time reinforcement. *Can J Physiol Pharmacol* **56:** 707–720, 1977.
2. Appel, J. B., J. A. Joseph, E. Utsey and L. L. Hernandez. Sensitivity to psychoactive drugs and the serotonergic neuronal system. *Commun Psychopharmacol* **1:** 541–551, 1977.
3. 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-methyl-amphetamine (DOM) and *d*-amphetamine on operant responding in control and 6-hydroxydopamine-treated rats. *Pharmacol Biochem Behav* **13:** 621–626, 1980.
4. Commissaris, R. L., K. E. Moore and R. H. Rech. Naloxone potentiates the disruptive effects of mescaline on operant responding in rats. *Pharmacol Biochem Behav* **13:** 601–603, 1980.
5. Commissaris, R. L., W. H. Lyness, K. E. Moore and R. H. Rech. Central 5-hydroxytryptamine and the effects of hallucinogens and phenobarbital on operant responding in rats. *Pharmacol Biochem Behav* **14:** 595–601, 1981.
6. Commissaris, R. L., W. H. Lyness, K. E. Moore and R. H. Rech. Differential antagonism by metergoline of the behavioral effects of indolealkylamine and phenethylamine hallucinogens in the rat. *J Pharmacol Exp Ther* **219:** 170–174, 1981.
7. Commissaris, R. L., D. J. Mokler, W. H. Lyness, K. E. Moore and R. H. Rech. The behavioral effects of hallucinogens in rats following 5,7-dihydroxytryptamine administration into the medial forebrain bundle. *Pharmacol Biochem Behav* **14:** 915–918, 1981.
8. Commissaris, R. L. and R. H. Rech. Antagonism of the behavioral effects of 2,5-dimethoxy-4-methylamphetamine (DOM) and quipazine by metergoline. *Pharmacol Biochem Behav* **15:** 659–682, 1981.
9. Dykstra, L. A. Effects of morphine, pentazocine and cyclazocine alone and in combination with naloxone on electric shock titration in the squirrel monkey. *J Pharmacol Exp Ther* **211:** 722–732, 1979.
10. Fink, M., J. Simeon, T. M. Itil and A. M. Freedman. Clinical antidepressant activity of cyclazocine—a narcotic antagonist. *Clin Pharmacol Ther* **11:** 41–48, 1969.
11. Gilbert, P. E. and W. R. Martin. The effects of morphine- and nalorphine-like drugs in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. *J Pharmacol Exp Ther* **198:** 66–82, 1976.
12. Harris, R. A. Interactions between narcotic agonists, partial agonists and antagonists evaluated by schedule-controlled behavior. *J Pharmacol Exp Ther* **213:** 497–503, 1980.

13. Henck, J. W. and R. H. Rech. Cyclazocine disruption of operant behavior involves both opioid and serotonergic components. *Pharmacologist* **24:** 116, 1982.
14. Holtzman, S. G. and R. E. Jewett. Stimulation of behavior in the rat by cyclazocine: Effects of naloxone. *J Pharmacol Exp Ther* **187:** 380–390, 1973.
15. Jasinski, D. R., W. R. Martin and J. D. Sapira. Antagonism of the subjective, behavioral, pupillary, and respiratory depressant effects of cyclazocine by naloxone. *Clin Pharmacol Ther* **9:** 215–222, 1967.
16. Martin, W. R., H. F. Fraser, C. W. Gorodetzky and D. E. Rosenberg. Studies of the dependence-producing potential of the narcotic antagonist 2-cyclopropylmethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (cyclazocine, WIN-20,740, ARCII-C-3). *J Pharmacol Exp Ther* **150:** 426–436, 1965.
17. Martin, W. R., C. W. Gorodetzky and T. K. McClane. An experimental study in the treatment of narcotic addicts with cyclazocine. *Clin Pharmacol Ther* **7:** 455–465, 1966.
18. Minnema, D. J., L. DeWitt and J. A. Rosecrans. Antinociceptive comparison of quipazine and morphine. *Communs Psychopharmacol* **4:** 115–120, 1980.
19. Mokler, D. J., R. L. Commissaris and R. H. Rech. Effects of 5-hydroxytryptamine (5-HT) antagonists, methergoline, cinanserin, and BC-105, on the disruption of operant behavior in rats following administration of hallucinogens. *Fed Proc* **40:** 267, 1981.
20. Rosecrans, J. A., W. T. Chance and R. M. Spencer. The discriminative stimulus properties of cyclazocine: Generalization studies involving nalorphine, morphine and LSD. *Res Commun Chem Pathol Pharmacol* **20:** 221–237, 1978.
21. Ruffing, D. M. and E. F. Domino. Effects of selected opioid agonists and antagonists on DMT- and LSD-25-induced disruption of food-rewarded bar pressing behavior in the rat. *Psychopharmacology* **75:** 226–230, 1981.
22. Samanin, R., S. Bernasconi and A. Quattrone. Antinociceptive action of quipazine: Relation to central serotonergic receptor stimulation. *Psychopharmacology (Berlin)* **46:** 219–222, 1976.
23. Steel, R. G. D. and J. H. Torrie. *Principles and Procedures of Statistics*. New York: McGraw-Hill, 1980.
24. Teal, J. J. and S. G. Holtzman. Discriminative stimulus effects of cyclazocine in the rat. *J Pharmacol Exp Ther* **212:** 368–376, 1980.
25. Tilson, H. A. and S. B. Sparber. Studies on the concurrent behavioral and neurochemical effects of psychoactive drugs using the push-pull cannula. *J Pharmacol Exp Ther* **181:** 387–398, 1972.
26. Tilson, H. A. and S. B. Sparber. Similarities and differences between mescaline, lysergic acid diethylamide-25 (LSD) and *d*-amphetamine on various components of fixed-interval responding in the rat. *J Pharmacol Exp Ther* **184:** 376–384, 1973.
27. White, J. M. and S. G. Holtzman. Three-choice drug discrimination in the rat: Morphine, cyclazocine and saline. *J Pharmacol Exp Ther* **217:** 254–262, 1981.
28. Zukin, R. S. and S. R. Zukin. Demonstration of [^{3}H]cyclazocine binding to multiple opiate receptor sites. *Mol Pharmacol* **20:** 254–264, 1981.