Pharmacology Biochemistry & Behavior, Vol. 27, pp. 385–389. © Pergamo Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Animal Models of Intravenous Phencyclinoid Self-Administration

K. L. MARQUIS AND J. E. MORETON[1]

Department of Pharmacology and Toxicology, School of Pharmacy
University of Maryland, 20 N. Pine St., Baltimore, MD 21201

MARQUIS, K. L. AND J. E. MORETON. *Animal models of intravenous phencyclinoid self-administration.* PHARMACOL BIOCHEM BEHAV 27(2) 385–389, 1987.—Phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP) self-administration has been demonstrated in rhesus monkeys, baboons, dogs and rats. Generally, an orderly inverted U-shaped dose-response curve for rates of self-injection has been observed. Total drug intake appears to increase slightly with increases in unit dose; however, this increase is much less than might be expected with other CNS depressants such as barbiturates or morphine. Additionally, several arylcyclohexylamine analogues of PCP and some members of the benzomorphan and dioxolane classes referred to collectively as "phencyclinoids" are self-administered by primates and dogs. New data are presented in this review profiling the self-administration of some of these drugs in rats, as well as a characterization of the self-administration of higher unit doses of PCP than previously reported. Also, preliminary results of the assessment of the reinforcing efficacy of some PCP analogues measured by the progressive ratio procedure are presented.

Phencyclidine Phencyclinoids Self-administration Review Progressive ratio Rat Primate Dog Reinforcement

PHENCYCLIDINE (1-(1-phenylcyclohexyl)piperidine, PCP), is recognized as a major drug of abuse [14]. The self-administration of PCP by laboratory animals was first reported in the early 1970's [1,21]. Studies since that time have demonstrated orderly dose-response relationships for the rate of PCP self-administration and the resulting level of drug intake in rhesus monkeys [1,21], baboons [15], beagle dogs [22] and rats [11]. While this review will focus on studies which have utilized the intravenous route of administration, it should be recognized that another important body of literature exists regarding the oral route of self-administration of PCP in rhesus monkeys (see references cited in [5,6]).

PCP possesses a unique profile of behavioral and pharmacological effects. It was originally developed for use as an anesthetic, but also possesses analgesic and anticonvulsant properties [18]. It stimulates locomotor behavior in rodents in addition to disrupting forced motor performance [18]. It also produces psychotomimetic effects in humans [14].

In recent years the opportunity to study the structure-activity relationship of these compounds relative to their reinforcing effects using the intravenous self-administration technique has been made possible by the availability of several structural analogues of PCP, an arylcyclohexylamine, from the National Institute on Drug Abuse. One analogue, ketamine, is synthesized and distributed by Parke-Davis, a division of Warner Lambert (Ketalar®, Morris Plains, NJ). These analogues possess PCP-like behavioral and pharmacological effects [25] and displace PCP from its receptor [30]. Similarly, compounds from the benzomorphan, benz(f)isoquinoline and dioxolane classes have been reported to produce PCP-like effects and displace PCP from its receptor [19]. We suggest that these compounds be referred to collectively as the "phencyclinoids" [18].

Early animal studies of intravenous PCP self-administration employed male rhesus monkeys having a history of psychomotor stimulant self-administration. In one report [21] subjects shown to self-administer cocaine were given limited access to three unit doses of PCP (0.025, 0.05, 0.1 mg/kg). The results were an orderly decrease in the number of PCP injections self-administered as the unit dose was increased with an increase in drug intake occurring at the high unit dose. At about the same time another report [1] extended these findings to a lower dose range (3.1–25 μg/kg/ing) using an FR10 schedule of reinforcement and included saline substitution as a vehicle control. All three of the rhesus monkeys tested self-administered at least three unit doses of PCP above the saline control range of responding, and the dose-response curves for rate of responding were of the typical inverted U shape. The total drug intake was generally positively related to the dose and was of a magnitude comparable to the anesthetic dose of PCP used in subhuman primates. During these self-administration sessions the subjects were often unable to maintain a sitting posture.

[1]Requests for reprints should be addressed to J. E. Moreton, Department of Pharmacology and Toxicology, University of Maryland School of Pharmacy, 20 N. Pine St., Baltimore, MD 21201.

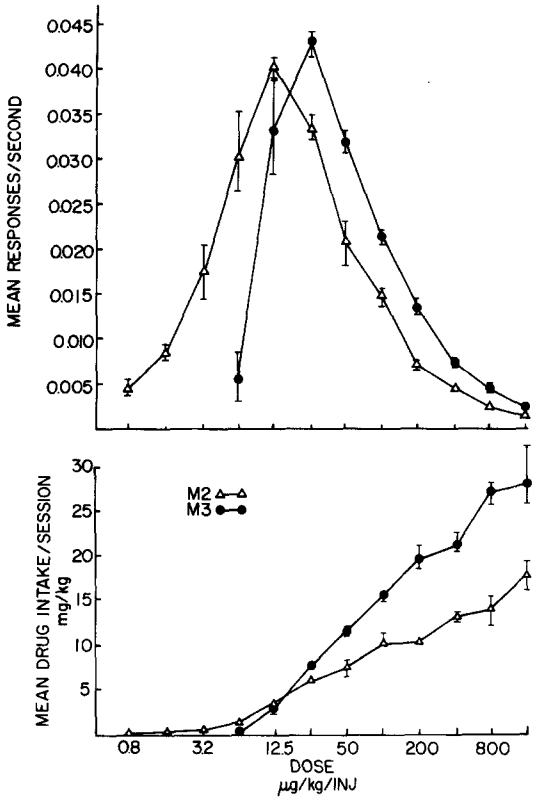

FIG. 1. Response rate (top panel) and drug intake (bottom panel) as a function of ketamine dose. Each data point represents the mean and range for the last 5 days (2 hours/day) of self-administration on a FR1 schedule of reinforcement. Absence of a vertical line at a particular point indicates that the range was within the area occupied by the symbol. Ordinate and abscissa are on linear and geometric scales, respectively. From: Moreton, J. E., R. A. Meisch, L. Stark and T. Thompson. Ketamine self-administration by the rhesus monkey. *J Pharmacol Exp Ther* **203**: 303–309, copyright by the American Society for Pharmacology and Experimental Therapy, 1977.

Early assessments of the reinforcing properties of ketamine reported that rhesus monkeys shown to self-administer methamphetamine [17] or cocaine [20] also self-administered ketamine (3.2–1600 μg/kg/inj) under limited access conditions at an FR1 schedule of reinforcement. Again, an inverted U-shaped dose-response curve was observed for rate of responding (Fig. 1). Also, drug intake was positively related to the unit dose. A variation of the fixed-ratio to about FR128 produced an orderly increase in the response rate and a decrease in drug intake. The magnitude of the change in drug intake, however, was only three-fold compared to a 128-fold increase in the response requirement.

These data for ketamine contrast with the effect of increasing the fixed-ratio on PCP self-administration. Drug-naive rhesus monkeys were reported to self-administer PCP (50 μg/kg/inj) at rates greater than saline when given 24 hour access on an FR1 schedule of reinforcement [1]. Increasing the schedule requirement to FR5, however, eliminated responding. Despite the procedural differences, the contrasting data for ketamine and PCP with respect to the effects of increasing the fixed ratio may indicate that ketamine, an analogue possessing greater depressant effects than PCP [16], is a more efficacious reinforcer. The self-administration of PCP in animal models may, therefore, be the result of the depressant effects rather than the psychotomimetic effects of the drug. Further direct comparisons between PCP and ketamine on measures of reinforcing efficacy are required.

TABLE 1

INJECTION RATES AND DRUG INTAKE OF PHENCYCLIDINE (PCP) AND PCP ANALOGUES SELF-ADMINISTERED BY THE RAT

Drug (mg/kg/inj)	Injection Rate (inj/hr)	Drug Intake (mg/kg/hr)
PCP		
0.5	2.68 ± 0.18	1.35 ± 0.09
1.0	1.66 ± 0.11	1.66 ± 0.10
2.0	1.06 ± 0.05	2.11 ± 0.10
KET		
1.56	12.02 ± 0.75	18.76 ± 1.17
3.12	6.73 ± 0.45	21.01 ± 1.40
6.25	3.39 ± 0.24	21.17 ± 1.50
TCPY		
0.25	4.47 ± 0.24	1.12 ± 0.06
0.5	2.71 ± 0.09	1.36 ± 0.05
1.0	1.94 ± 0.06	1.94 ± 0.06
PCE		
0.25	4.90 ± 0.45	1.23 ± 0.14
0.5	2.88 ± 0.34	1.44 ± 0.17
1.0	1.41 ± 0.11	1.41 ± 0.11

The data (from [11]) presented are the mean (±S.E.M.) of four sessions in four rats. The same four rats were exposed to all doses and drugs.

Abbreviations: PCP, phencyclidine, 1-(1-phenylcyclohexyl)piperidine HCl; TCPY, 1-(1-(2-thienyl)cyclohexyl)pyrrolidine HCl; PCE, N-ethyl-1-phenylcyclohexylamine HCl; KET, ketamine, 2-(o-chlorophenyl)-2-methylaminocyclohexanone HCl.

Intravenous self-administration studies have now been extended to other phencyclinoids and to other animal species. Beagle dogs, experienced with the self-administration of both psychomotor stimulants and sedative-hypnotics, will also self-administer PCP under limited-access conditions [22]. Several analogues and two metabolites are also self-administered in a qualitatively similar fashion. Interestingly, the relative rank-ordering of the potencies of these compounds in the self-administration procedure in the dog correlates significantly with the rank-ordering of potency in a number of other pharmacologic assays including PCP receptor binding [13] and the rat drug discrimination paradigm [23]. Thus, the differences in the self-administration of phencyclinoids appear initially to be due mainly to differences in potency, a finding consistent with that of other investigators comparing PCP with these arylcyclohexylamines on behavioral and pharmacological effects [9].

Self-administration studies of the phencyclinoids benzomorphans and dioxolanes reveal an isomeric separation of activity. When substituted for cocaine, PCP and the (+)-isomer of N-allylnormetazocine (+-SKF 10,047) and cyclazocine is self-administered by rhesus monkeys; the racemate and the (−)-isomer of these compounds, however, are not [24]. The dextrorotary dioxolane, dexoxadrol, and the ethyl-substituted analogue, etoxadrol, are also self-administered [4]. There are no reports of the self-administration of the levorotary dioxolane isomer, levoxadrol.

These data parallel the results of drug discrimination studies. Both rats and squirrel monkeys trained to discrimi-

nate PCP from saline generalize the cue to (+)-N-allylnormetazocine and the racemate while the (−)-isomer does not generalize [3]. Squirrel monkeys generalize a PCP training stimulus to the (+)-isomer of cyclazocine, but not the racemate or the (−)-isomer [2]. Dexoxadrol, but not levoxadrol, produces drug-lever responding in rhesus monkeys trained to discriminate ketamine from saline [29]. Also, etoxodrol produces PCP-lever responding in rhesus monkeys trained to discriminate PCP from saline [4]. These data indicate that compounds sharing similar stimulus properties may also exhibit the reinforcing properties of this pharmacological class.

While the aforementioned data have established that PCP and related compounds are self-administered by non-human primates and dogs, relatively little data exist to date on the self-administration of phencyclinoids in the rat. In one report [7] male Wistar rats were trained to intravenously self-administer a 0.125 mg/kg unit dose of PCP in 24-hr access sessions. Of the six drug-naive rats tested, three readily began self-administration at this unit dose while three did not. However, when food deprived, all of the rats increased lever pressing for drug. These results were not a function of a generalized increase in activity of the rat produced by the food-deprived state as evidenced by the lack of increased responding on a second dummy lever in the chamber.

In another report [8] drug-naive female Sprague-Dawley rats were given access initially to saline (3 days), then a unit dose of PCP (5 days) and finally another dose of PCP 0.5 log units lower than the original dose (5 days). For each rat a score ranging from 0 to 3 was given at the end of the procedure to rank the original unit dose for reinforcing activity based on whether the number of injections obtained for the original dose and/or the lower dose exceeded saline injections. Of the three unit doses of PCP tested, the highest dose of 0.32 mg/kg produced a score of 1 in all 7 subjects. Lower doses were ineffective in some or all subjects. A unit dose of 1.0 mg/kg of ketamine produced a similar ranking of reinforcing activity.

These two early studies indicate that PCP and probably PCP analogues are self-administered by the rat. We have expanded these studies in the rat to include the testing of larger doses of PCP and include more of the PCP analogues known to be self-administered by other species. In addition to profiling the dose-response curves for rates of self-administration of PCP and 3 PCP analogues, we are in the process of assessing the relative reinforcing efficacy of drugs from this class using a progressive ratio procedure. The following represents an overview of the self-administration study and the preliminary findings on the progressive ratio procedure.

METHOD

The drugs selected for study were PCP, ketamine (2)(o-chlorophenyl)-2-methylaminocyclohexanone HCl, KET), 1-(1-phenylcyclohexyl)pyrrolidine HCl (PCPY), 1-(1-(2-thienyl)cyclohexyl)piperidine HCl (TCP), 1-(1-(2-thienyl)cyclohexyl)pyrrolidine HCl (TCPY), and N-ethyl-1-phenylcyclohexylamine HCl (PCE). Ketamine (Ketalar®) was obtained from Parke-Davis, a division of Warner Lambert (Morris Plains, NJ). All other test drugs were supplied by the National Institute on Drug Abuse. They were diluted with saline and doses were calculated on the basis of the salt.

Female Sprague-Dawley rats (250–300 g, Dominion Laboratories, Dublin, VA, N=4), were housed individually in standard plastic shoe-box cages on San-i-cell® bedding and maintained with food and water available ad lib in a temperature-controlled laboratory (72°F) with illumination from 06:00 to 22:00. They were prepared with chronic jugular cannulae according to a previously reported method [27] under Chloropent® anesthesia (1 ml per 50 g of body weight, Fort Dodge Laboratories, Fort Dodge, IA). During the period of illumination, the subjects were placed in custom-made Plexiglas® chambers (66 cm H × 29 cm W × 29 cm D) with water but not food available. A single operant lever (BRS/LVE) was mounted on one wall of the chamber. The subjects were trained to self-administer cocaine HCl (1.0 mg/kg/inj; Sigma Chemical Co., St. Louis, MO) under an FR10 schedule of reinforcement. In addition to using the intermittent schedule, a protective device surrounding the operant lever was added to prevent inadvertant lever presses which might occur under the effects of cocaine or the phencyclinoids. After the training phase, KET (1.56 or 3.12 mg/kg/inj) was substituted for cocaine. Once stable self-administration of KET was established, three unit doses of PCP, KET, PCE and TCPY were tested in limited access sessions 2–10 hours in length. Self-administration of each unit dose of PCP or PCP analogue was monitored for four days prior to proceeding to the next unit dose. All unit doses of a drug were completed prior to proceeding to the next drug.

In preliminary experiments, reinforcing efficacy was assessed using female Sprague-Dawley rats (N=8) trained to self-administer cocaine as described above. After training, cocaine was replaced with various doses of KET (N=3), TCP (N=1) or PCPY (N=3). Once self-administration of the initial test dose had stabilized for four sessions, a progressive ratio test was imposed. Other unit doses lower than the initial dose were tested after stabilization of self-administration at that dose. Two to three replications were obtained for some doses. Various doses of cocaine (N=1) were assessed using the same test.

In the progressive ratio test session, the response requirement for each successive reinforcement was incremented according to an empirically-determined formula previously described [28]. The initial increment (step) in the progression is somewhat less than a doubling (0.2 log units or 1.58×) and this factor is decreased by 4.5% with each step in the progression. The resulting progressive ratio (PR) follows: 1, 2, 3, 4, 6, 8, 12, 17, 23, 32, 44, 58, 77, 100, 129, ... This gradual change in response requirement allows for a better resolution of the breaking point, the progression step at which the rat failed to complete the prescribed ratio within a two hour time limit. Since the rats had been trained on an FR10 schedule, the progression in these tests began at PR12 and then proceeded along the progression shown above. The programming equipment employed (Ledger Technical Services, Kalamazoo, MI) limits the maximum ratio to 939 responses, or 19 progression steps.

RESULTS

The mean injection rate and intake for the four drugs tested under the FR10 schedule of reinforcement are shown in Table 1. For each drug geometric increases in dose produced linear decreases in injection rate [repeated measures ANOVA, PCP: $F(2,6)=27.7$; KET: $F(2,6)=40.4$; PCE: $F(2,6)=17.8$; TCPY: $F(2,6)=29.3$, $p<0.01$ for all]. A relatively constant rate of self-administration was typical for each drug and each dose tested, and the interinjection interval increased systematically with each increase in dose. At

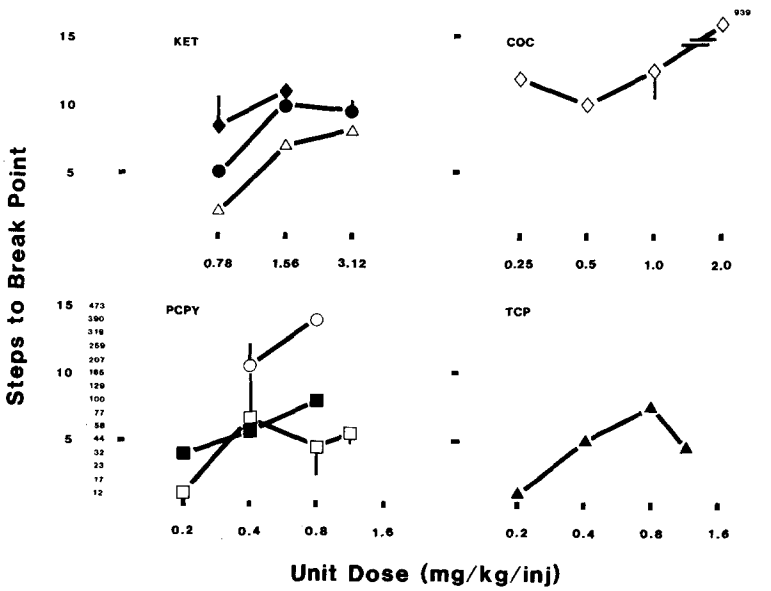

FIG. 2. Steps to the breaking point as a function of dose of KET (ketamine HCl), COC (cocaine HCl), PCPY (1-(1-phenylcyclohexyl)pyrrolidine HCl), or TCP (1-(1-(2-thienyl)cyclohexyl)piperidine HCl). Each line represents the data from a single subject. Vertical lines are the standard error of the mean of two or three determinations. The ordinate and abscissa are linear and geometric scales, respectively. The actual ratio at each step is labeled on the ordinate of the lower left panel.

each dose the operant behavior remained under schedule control with the majority of the responses required for reinforcement occurring immediately prior to the injection. Drug intake increased slightly with increases in dose for PCP and TCPY [repeated measures ANOVA, $F(2,6)=69.6$, $F(2,6)=125.2$, $p<0.001$, respectively]. The drug intake did not vary with dose for ketamine and PCE.

The results of preliminary investigations of reinforcing efficacy using the progressive ratio test are presented in Fig. 2. Maximal breaking points of PR77 and PR100 were obtained in two of the three rats tested under PCPY and in the one rat tested under TCP. A maximal breaking point of PR390 was obtained in one rat under PCPY. Ketamine produced maximal breaking points of PR165 in two of the three rats tested. Lower doses of each drug produced lower breaking points. All doses of cocaine, on the other hand, produced breaking points of PR165 or greater in the one rat tested.

DISCUSSION

Some differences exist between the overt behavioral response observed during the self-administration of the phencyclinoids by primates and dogs in contrast with rodents. For example, monkeys self-administering PCP seldom exhibit behavioral excitation and at sufficiently high doses self-administer the drug to the point of producing anesthesia [1]. Rodents show excitatory effects during self-administration evidenced by intense circling, stereotypic sniffing, and head weaving [11]. At high unit doses severe ataxia and momentary loss of consciousness can occur. On the other hand, PCP supports lever-press behavior under intermittent schedules of reinforcement in all three species. In general, drug intake tends to increase slightly with increases in unit dose for each species. However, the increase is of a lesser degree than generally occurs with the self-administration of other CNS depressants such as pentobarbital [10] or morphine [28].

The rank-ordering of potency of these compounds for rates of self-administration are similar for monkeys, dogs and rats. One notable difference is that rats appear to be less sensitive to the drug. PCP self-administration in dogs and monkeys occurs from 6 to 50 μg/kg/injection. On the other hand, a dose of 0.032 mg/kg/injection of PCP fails to support self-administration in drug-naive rats [8]. Lower doses of PCP than the doses reported here (0.5–2.0 mg/kg/injection) have yet to be tested using a substitution procedure in rats.

In addition to addressing the question of reinforcing potency of PCP and PCP analogues in rats, preliminary investigations are in progress to assess the reinforcing efficacy of some phencyclinoids using the progressive ratio procedure. The initial results presented here indicate that while PCP analogues may not be as reinforcing as some doses of cocaine, they can maintain relatively high rates of responding. To date, these tests have not revealed differences between phencyclinoids with respect to reinforcing efficacy.

In summary, a number of studies have shown that laboratory animals will self-administer PCP and PCP related compounds. These results support the observation that many of the drugs that humans abuse are self-administered by laboratory animals [12]. The availability of structural analogues of PCP and the fact that at least two different classes of compounds share PCP's effects in this model have allowed the study of the structure activity relationships and stereospecificity of phencyclinoid abuse potential. Despite the differences observed between primates, dogs, and rodents, the validation of the self-administration of the phencyclinoids in rats provides the means for expanding the studies to investi-

gate the behavioral, biochemical and neurophysiological correlates of phencyclinoid self-administration and may lead to a better understanding of the neuropsychopharmacological basis of the abuse potential of phencyclinoids.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the expert technical assistance of Mr. Michael G. Webb and Mr. Michael Gentry. The animal facility at UMAB is AAALAC approved. This research was supported by NIDA Grant DA 03173. Dr. Marquis is a NIDA postdoctoral fellow.

REFERENCES

1. Balster, R. L., C. E. Johanson, R. T. Harris and C. R. Schuster. Phencyclidine self-administration in the rhesus monkey. *Pharmacol Biochem Behav* **1:** 167–172, 1973.
2. Brady, K. T. and R. L. Balster. Discriminative stimulus properties of stereoisomers of cyclazocine in phencyclidine-trained squirrel monkeys. *Life Sci* **31:** 541–549, 1982.
3. Brady, K. T., R. L. Balster and E. L. May. Stereoisomers of N-allylnormetazocine: Phencyclidine-like behavioral effects in squirrel monkeys and rats. *Science* **215:** 178–180, 1982.
4. Brady, K. T., W. L. Woolverton and R. L. Balster. Discriminative stimulus and reinforcing properties of etoxadrol and dexoxadrol in monkeys. *J Pharmacol Exp Ther* **220:** 56–62, 1982.
5. Carroll, M. E. Concurrent phencyclidine and saccharin access: Presentation of an alternative reinforcer reduces drug intake. *J Exp Anal Behav* **43:** 131–144, 1985.
6. Carroll, M. E. Performance maintained by orally delivered phencyclidine under second-order, tandem and fixed-interval schedules in food-satiated and food-deprived rhesus monkeys. *J Pharmacol Exp Ther* **232:** 351–359, 1985.
7. Carroll, M. E., C. P. France and R. A. Meisch. Intravenous self-administration of etonitazene, cocaine and phencyclidine in rats during food deprivation and satiation. *J Pharmacol Exp Ther* **217:** 241–247, 1981.
8. Collins, R. J., J. R. Weeks, M. M. Cooper, P. I. Good and R. R. Russell. Prediction of abuse liability of drugs using iv self-administration by rats. *Psychopharmacology (Berlin)* **82:** 6–13, 1984.
9. Cone, E. J., R. L. McQuinn and H. E. Shannon. Structure-activity relationship studies of phencyclidine derivatives in rats. *J Pharmacol Exp Ther* **228:** 147–153, 1984.
10. Goldberg, S. R., F. Hoffmeister, U. U. Schlichting and W. Wuttke. A comparison of pentobarbital and cocaine self-administration in rhesus monkeys: Effects of dose and fixed ratio parameter. *J Pharmacol Exp Ther* **179:** 227–283, 1971.
11. Goodman, N. L. and J. E. Moreton. Phencyclidine (PCP) and PCP analogue self-administration in the rat. *Pharmacol Biochem Behav,* submitted.
12. Griffiths, R. R., G. E. Gigelow and J. E. Henningfield. Similarities in animal and human drug taking behavior. In: *Advances in Substance Abuse: Behavioral and Biological Research,* edited by N. K. Mello. Greenwich, CT: JAI Press, Inc., 1980, pp. 1–90.
13. Jasinski, D. R., H. E. Shannon, E. J. Cone, D. B. Vaupel, M. E. Risner, R. L. McQuinn, T. P. Su and W. B. Pickworth. Interdisciplinary studies on phencyclidine. In: *PCP (Phencyclidine): Historical and Current Perspectives,* edited by E. F. Domino. Ann Arbor, MI: NPP Books, 1981, pp. 331–400.
14. Lerner, R. L. and R. S. Burns. Phencyclidine use among youth: History, epidemiology, and acute and chronic intoxication. *Natl Inst Drug Abuse Res Monogr Ser* **21:** 66–118, 1978.
15. Lukas, S. E., R. R. Griffiths, J. V. Brady and R. M. Wurster. Phencyclidine-analogue self-administration by the baboon. *Psychopharmacology (Berlin)* **83:** 316–320, 1984.
16. McCarthy, D. A., G. Chen, D. H. Kaump and C. Ensor. General anesthetic and other pharmacological properties of 2-(o-chlorophenyl)-2-methylamino cyclohexanone HCl (CI-581). *J New Drugs* **5:** 21–33, 1965.
17. McCarthy, D. A., Jr. and S. E. Harrigan. Dependence-producing capacity of ketamine in *Macaca mulatta.* In: *Anaesthesiology: Proceedings of the VI World Congress of Anaesthesiology,* Mexico City, April, 1976, edited by E. Hulsz, J. A. Sanchez-Hernandez, G. Vasconcelos and J. N. Lunn. Amsterdam: Excerpta Medica, 1977, pp. 160–168.
18. Mattia, A., A. P. Leccese, K. L. Marquis, E. E. El-Fakahany and J. E. Moreton. Electroencephalographic (EEG), psychopharmacological, and receptor-binding profiles of "phencyclinoids." *Natl Inst Drug Abuse Res Monogr Ser* **64:** 94–111, 1986.
19. Mendelsohn, L. G., G. A. Kerchner, V. Kalra, D. M. Zimmerman and J. D. Leander. Phencyclidine receptors in rat brain cortex. *Biochem Pharmacol* **33:** 3529–3535, 1984.
20. Moreton, J. E., R. A. Meisch, L. Stark and T. Thompson. Ketamine self-administration by the rhesus monkey. *J Pharmacol Exp Ther* **203:** 303–309, 1977.
21. Pickens, R., T. Thompson and D. C. Muchow. Cannabis and phencyclidine self-administration by animals. In: *Bayer-Symposium IV, Psychic Dependence,* edited by L. Goldberg and F. Hoffmeister. New York: Springer-Verlag, 1973, pp. 78–86.
22. Risner, M. E. Intravenous self-administration of phencyclidine and related compounds in the dog. *J Pharmacol Exp Ther* **221:** 637–644, 1982.
23. Shannon, H. E. Evaluation of phencyclidine analogs on the basis of their discriminative properties in the rat. *J Pharmacol Exp Ther* **216:** 543–551, 1981.
24. Slifer, B. L. and R. L. Balster. Reinforcing properties of stereoisomers of the putative sigma agonists N-allylnormatazocine and cyclazocine in rhesus monkeys. *J Pharmacol Exp Ther* **225:** 522–528, 1983.
25. Vaupel, D. B., D. McCoun and E. J. Cone. Phencyclidine analogs and precursors: Rotarod and lethal dose studies in the mouse. *J Pharmacol Exp Ther* **230:** 20–27, 1984.
26. Weeks, J. R. and J. R. Collins. The progressive ratio method for evaluating strength of reinforcement of IV self-administered drugs using rats. Presented at the satellite meeting of ISGIDAR during the meeting of the Committee on Problems of Drug Dependence, Baltimore, MD, June, 1985.
27. Weeks, J. R. and J. D. Davis. Chronic intravenous cannulas for rats. *J Appl Physiol* **85:** 540–551, 1964.
28. Woods, J. H. and C. R. Schuster. Reinforcement properties of morphine, cocaine and SPA as a function of unit dose. *Int J Addict* **3:** 231–237, 1968.
29. Young, A. M., S. Herling, G. D. Winger and J. H. Woods. Comparison of discriminative and reinforcing effects of ketamine and related compounds in the rhesus monkey. *Natl Inst Drug Abuse Res Monogr Ser* **34:** 173–179, 1981.
30. Zukin, S. R. and R. S. Zukin. Specific [^{3}H]phencyclidine binding in rat central nervous system. *Proc Natl Acad Sci USA* **76:** 5372–5376, 1979.