Psychopharmacology (1984) 83:316–320

Psychopharmacology

Original investigations

Phencyclidine-analogue self-injection by the baboon

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Abstract. Self-injection of phencyclidine HCl (PCP) and four of its analogues was examined in baboons. IV injections of drug were dependent upon completion of 160 lever presses (a 160-response fixed-ratio schedule). A 3-h time-out period followed each injection, permitting a maximum of eight injections per day. Self-injection performance was first established with cocaine and, once stable, test doses of each drug were substituted for 15 days. All five compounds maintained maximal self-injection performance, differing only in their relative potencies. The order of potency was approximately PCP > NMPCA = TCPY > NNBPCA > ketamine. Analysis of the distribution of injections throughout the day indicate that lower doses (and vehicle) were injected mainly during the daylight hours (i.e., 9AM–6 PM), but as the dose was increased the injections became more uniformly distributed. Only the highest doses of these compounds affected food intake, though the degree of suppression was modest. No differences between these compounds with respect to their abuse potential could be found.

Key words: Drug self-administration – Cocaine – Phencyclidine – Ketamine – PCP analogues – Baboons

The development and refinement of animal drug self-administration procedures has provided a method for assessing the reinforcement effectiveness of drugs. Application of the results from such studies has established a basis for providing information relevant to human abuse potential. A substantial body of data demonstrates that animals will self-administer drugs that are abused by humans (Griffiths et al. 1979b, 1980a; Johanson and Balster 1978). In this regard, phencyclidine (PCP) has been shown to be self-administered orally in monkeys (Carroll and Meisch 1980) and IV in monkeys (Balster et al. 1973; Pickens et al. 1973), dogs (Jasinski et al. 1979), and rats (Carroll et al. 1981). In addition, Balster and Woolverton (1980) demonstrated that, under conditions of continuous drug access, monkeys will self-administer PCP at levels that produce physical dependence.

Relative to other drugs of abuse, PCP is easily synthesized and, as a result, clandestine laboratories have been created for the sole purpose of making PCP (Shulgin and MacLean 1976). The U.S. Drug Enforcement Agency has attempted to curtail the illicit synthesis of PCP by placing piperidine (a major constituent of the process) under Schedule II control. Unfortunately, numerous amines can be substituted for piperidine in the process and the illegal laboratories have utilized this strategy to synthesize new PCP analogues. Many of these analogues have already appeared in confiscated street samples of what was claimed to be PCP (Bailey et al. 1976; Shulgin and MacLean 1976; Cone et al. 1979; Smialek et al. 1979).

In general, studies on the structure-activity relationships of PCP analogues have demonstrated a good correlation between receptor binding potencies and pharmacological effects (Kalir et al. 1969, 1978; Vincent et al. 1979). In addition, Shannon (1981) has demonstrated that the discriminative-stimulus properties of numerous PCP analogues are similar to those produced by PCP in rats. This suggests that these analogues may possibly share PCP's reinforcing properties as well. Ketamine, a shorter-acting analogue of PCP, has also been shown to be self-administered in animals (McCarthy and Harrigan 1977; Moreton et al. 1977) and Risner (1982) has reported that dogs will self-inject numerous PCP analogues during short daily sessions.

The present study was undertaken to assess the reinforcing properties of PCP and four analogues in baboons under relatively large fixed-ratio (FR) schedules (i.e., FR 160) and during 24-h access to the drugs. These analogues were selected to test a short- versus long-chain substitution on the nitrogen and to test a replacement of the phenyl ring and the piperidine moieties by a thienyl and a pyrrolidine, respectively.

Materials and methods

Eight male baboons (*Papio anubis*) weighing 18–28 kg were subjects. Animals TU, NL, and OM were drug-naive at the start of the study while the other baboons had histories of drug self-administration with a variety of compounds (e.g., amphetamine, methohexital, amobarbital, butorphanol, ethanol). Prior to drug testing all animals had received lever-pressing training on a FR-160 schedule. Throughout the experiments animals had continuous access to water (via a drinking tube) and food pellets (as described). In addition, they received daily rations of fresh fruit.

Housing. Each animal was adapted to a standard restraint chair (Findley et al. 1971) or a harness-tether restraint system (Lukas et al. 1982). Chair-restrained animals were

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housed individually in a sound-attenuated chamber ($0.8 \times 1.2 \times 1.2$ m). Harness-tether-restrained animals were individually housed in standard primate 'squeeze' cages ($0.75 \times 0.91 \times 1.18$ m), which were enclosed in sound-attenuated chambers. Extraneous sounds were further masked by continuous white noise. A 0.7×1.0 m intelligence panel was mounted at the rear of each chamber upon which the levers, jewel lights, and a food hopper were attached. The food lever was located in the lower right side of the panel and pellets (1 g Noyes or Bio-Serv) were available under a FR-30 schedule. Additional features of the panel have been described in a previous report (Griffiths et al. 1975).

IV catheterization. Under pentobarbital anesthesia (15 mg/kg IV), each animal was surgically prepared with a jugular or femoral venous Silastic catheter (ID 0.79 mm, OD 2.36 mm), using the general procedures described by Lukas et al. (1982) and Lukas (1983). The catheter passed SC and exited in the middle of the back. If a catheter became defective the animal was prepared with a replacement catheter using the same procedures. A detailed description of the injection system has been presented previously (Findley et al. 1972). Briefly, the catheter was attached to a valve system that allowed slow continuous administration (approximately 100 ml/24 h) of heparinized saline (5 IU/ml) via a peristaltic pump (Harvard 1201) to maintain catheter patency. Drug was injected into the valve system by means of a second pump and then flushed into the animal with saline from a third pump. This system necessitated a delay of approximately 20 s between onset of drug delivery and actual injection into the vein. All drugs were delivered within a 2-min period. The total volume of fluid delivered during each injection was 10 ml (5 ml drug solution followed by 5 ml saline).

Procedure. The availability of an injection was indicated by a 5-s tone and illumination of a jewel light (approximately 1.5-cm diameter) directly over a Lindsley lever (R. Gerbrands, Arlington, MA) located slightly to the left of center near the bottom of the intelligence panel. When the light was illuminated, each response produced a brief feedback tone (approximately 0.1 s) and upon completion of a FR-160 response schedule requirement, the light over the lever was extinguished, the drug injection began, and a 5×5 cm light was illuminated in the upper left-hand corner of the intelligence panel for a 1-h period. A time-out period of 3 h followed each injection, permitting a maximum of eight injections per day. There was no time limit for completion of the FR-160 response requirement. Data was collected each day at 10 AM and drug changes were made at this time, if indicated.

Self-injection performance was first established with cocaine at a dose of 0.32 mg/kg. After 3 consecutive days of cocaine availability during which six or more injections were taken each day, a dose of test drug or vehicle was substituted for the cocaine for a period of 15 days. Cocaine was then reinstated and, when the criterion of 3 consecutive days of six or more injections per day had been met (typically 3–5 days), another dose of a test drug was substituted. This procedure of replacing cocaine with a test drug was continued throughout the study.

For any given drug the order of exposure to different doses was usually an ascending sequence. There were, however, occasions on which lower doses were examined after higher doses. The drug vehicle was generally examined immediately before or after the series of doses. For animals tested on several different compounds, the order of exposure to the compounds was arbitrary.

Overall response rates for each animal were determined by dividing the number of responses by the total time of drug availability during the last 5 days of the 15-day period. Relative potencies and analyses of parallelism of the dose-response curves for injection-per-day data were calculated using standard bioassay techniques (Finney 1964).

Drugs. The following drug doses (expressed as mg/kg/injection of the salt) were studied: cocaine HCl (0.32); phencyclidine HCl (0.01, 0.032, 0.1, 0.32); ketamine HCl (0.01, 0.032, 0.1, 0.32, 1.0); *N*-methyl-1-phenylcyclohexylamine HCl (NMPCA; 0.0032, 0.01, 0.032, 0.1, 0.32); 1-(*n*-butyl)-1-phenylcyclohexylamine HCl (NNBPCA; 0.01, 0.032, 0.1, 0.32, 1.0); 1-[1-(2-thienyl) cyclohexyl] pyrrolidine HCl (TCPY; 0.01, 0.032, 0.1, 0.32). The vehicle for NNBPCA was 0.5% ethanol in 0.9% NaCl, while the vehicle for all other drugs was 0.9% NaCl.

Results

Self-injection performance. Figure 1 shows the mean number of injections during the final 5 days for PCP, ketamine, NMPCA, NNBPCA, and TCPY. Cocaine generally maintained self-injection levels of seven to eight injections per day, while values for vehicle were zero to three per day. Low doses (0.01 – 0.032 mg/kg) of all drugs were associated with self-injection levels similar to vehicle control, while increasing doses were generally associated with increasing numbers of injections per day. PCP was the most potent compound with respect to number of injections and was approximately 1.5 times more potent than TCPY and NMPCA, three times more potent than NNBPCA, and 15 times more potent than ketamine. These relationships observed with number of injections per day also generally held true for response rates. Response rates for vehicle and low doses of all drugs were typically 0.003 – 0.006 responses/s. Response rates increased to 0.25 – 0.45 responses/s as the dose was increased for all compounds except TCPY, which were approximately 0.07 responses/s. The maximal rates of responding maintained by PCP and its analogues were similar to those maintained by 0.32 mg/kg cocaine and were 0.24 – 0.46 responses/s.

The local pattern of drug-maintained responding with cocaine and the higher doses of PCP and its analogues (0.1 – 0.32 mg/kg) was typical of that generated by FR schedules maintained by other types of reinforcers. During the time-out period, little or no responding occurred. Onset of drug availability (i.e., presentation of tone and light) was associated with an initial period of pausing, followed by responding at rather high, stable rates (greater than 1 response/s) until completion of the FR requirement. The local patterns associated with vehicle and lower doses of these compounds were characterized by substantially more pausing and bursts of responding. However, when runs of responses occurred, they generally continued at rates greater than 1 response/s.

The injection distribution of cocaine, saline, and various doses of PCP over a 24-h period is shown in Fig. 2. The self-injections of cocaine, typically eight per day, generally were

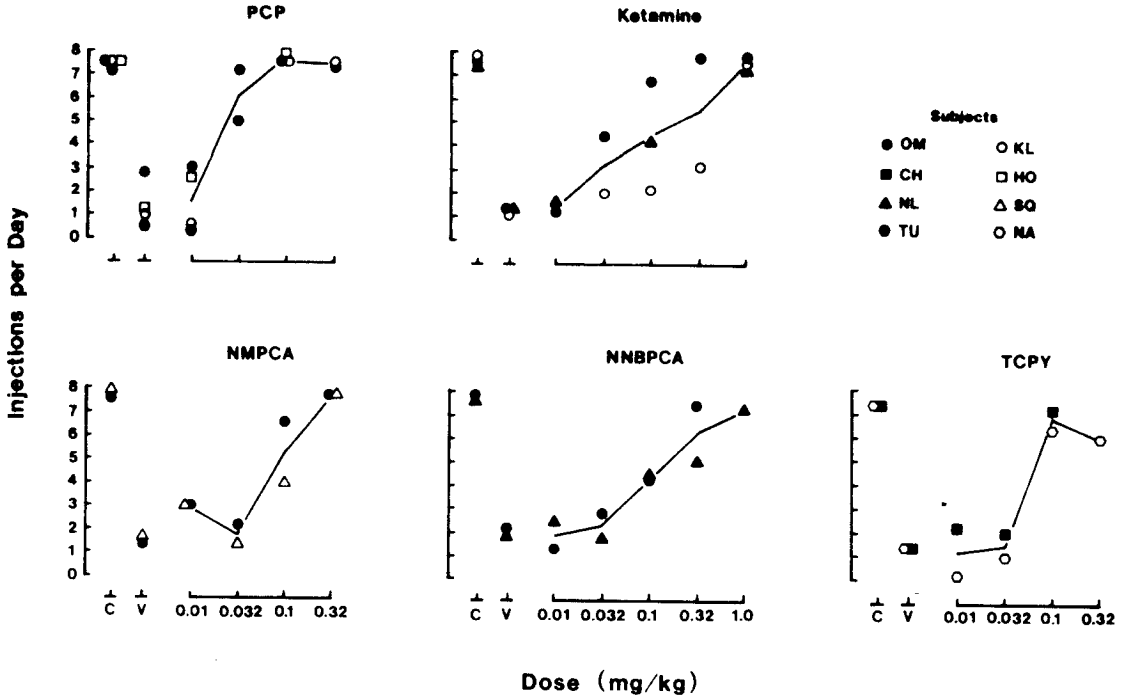

Fig. 1. Mean number of injections per day maintained by PCP, ketamine, NMPCA, NNBPCA, and TCPY: *Y-axis* injections per day; *X*-axis dose (mg/kg/injection), log scale; *C* indicates mean number of cocaine self-injections per day obtained from the 3-day periods that immediately preceded every substitution of a drug dose or vehicle; *V* indicates mean of the final 5 days after substitution of the drug vehicle. Drug data points indicate mean of the last 5 days after substitution of a drug dose. Lines connect means at indicated doses of drug. Different symbols designate individual animals

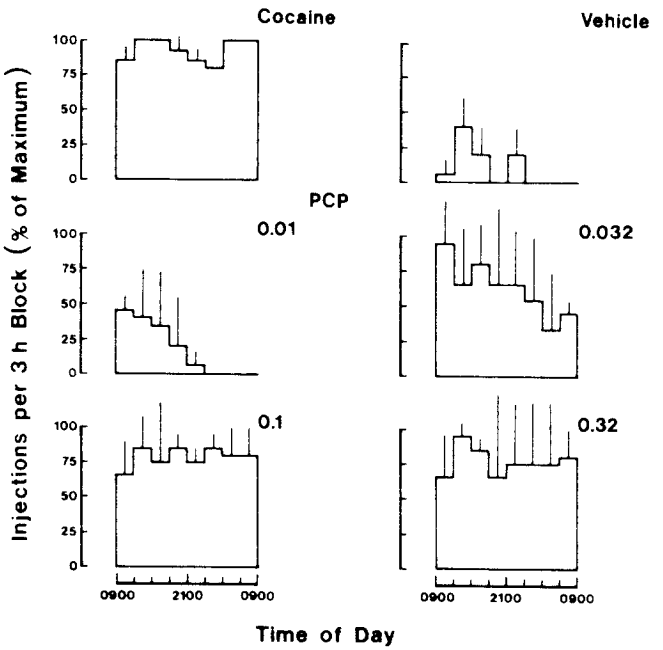

Fig. 2. Distribution of injections during a 24-h period for cocaine, saline, and various doses (mg/kg/injection) of PCP in baboons TU, KL, and OM. Data were obtained during cocaine control periods and the final 5 days after substitution of vehicle or a dose of PCP. Data were derived by dividing the number of injections taken in each of the 3-h bins by the maximally available number of injections in that bin during the 5-day period (1 injection/3-h bin × 5 days × 3 animals = 15 possible injections per bin). These values were then converted to percentages. *Bars* indicate means in successive 3-h bins; *vertical* lines represent 1 SD

uniformly distributed throughout the day. In contrast, self-injections of saline occurred between 9 AM and 5 PM (an occasional injection occurring between 9 PM and 12 midnight) with little or no responding occurring during the late-night or early-morning hours. The distribution of PCP injections was dose-related, with low doses showing a profile like that obtained with saline (i.e., fewer injections per day and only during the morning and early afternoon). As the dose was increased, the distribution of injections became more uniform throughout the day, thus, resembling the profile obtained with cocaine. The four analogues ketamine, TCPY, NMPCA, and NNBPCA all demonstrated dose-related self-injection profiles that resembled those of PCP (data not shown).

Throughout drug testing animals were periodically observed for gross behavioral changes after an injection. No obvious behavioral changes occurred during exposure to the experimental drug doses of 0.01 – 0.032 mg/kg, the vehicles, and the standard cocaine dose. The highest dose (0.32 mg/kg) of PCP and NMPCA were, however, associated with clear signs of sedation and ataxia. Doses higher than those reported in this study were tested, but none were replicated because of toxic effects (e.g., intense agitation, extreme muscle rigidity). During self-administration of all five compounds, food intake was generally unaffected by the lower doses and somewhat suppressed (10% – 25%) at higher doses.

Discussion

The present study demonstrated that PCP and four of its analogues maintained self-injection behavior in the baboon.

Daily injections and response rates increased as a function of dose and the higher doses of all compounds maintained numbers of injections and response rates similar to those maintained by cocaine (0.32 mg/kg/injection). The finding that PCP is a reinforcer is consistent with previous studies (Balster et al. 1973; Pickens et al. 1973). Moreover, ketamine (Moreton et al. 1977) and other analogues (Risner 1982) have also been shown to maintain self-injection performance in monkeys and dogs, respectively.

The finding in the present study that response rates increased with increasing dose is in contrast with previous studies using PCP (Pickens et al. 1973; Balster et al. 1973), ketamine (Moreton et al. 1977), and numerous PCP analogues (Risner 1982) as reinforcers. The rate-decreasing effects of these drugs demonstrated in these other studies most likely arises from the use of schedules which impose only a brief or no time-out period after each injection. In the present study a 3-h time-out period followed each injection and may have attenuated or eliminated the descending limb of the dose-response curve by allowing the animals time to recover from the direct effects of the previous injection. Very high (e.g. 1.0 – 3.2 mg/kg) unit doses, however, caused intense toxic reactions and were not replicated. A similar relationship between injection frequency and time-out duration has been noted for cocaine and sedative-hypnotics (Griffiths et al. 1979b, 1981).

The relative potencies of these PCP analogues with respect to maintaining self-administration behavior correspond well with the reported potency values using other behavioral and physiologic measures. For example, Shannon (1981) found that NMPCA was approximately equipotent with PCP in producing discriminative stimuli in rats: TCPY was about 0.9-times as potent as PCP, while NNBPCA and ketamine were 0.3- and 0.1-times as potent, respectively, in producing PCP-like discriminative stimuli. A similar profile of relative potencies has been demonstrated in PCP binding assays (Jasinski et al. 1981; Hampton et al. 1982). In these studies, compounds with *N*-substitutions of large alkyl chains (e.g., NNBPCA) were less potent than those with small chain substitutions (e.g., NMPCA) in a variety of in vivo and in vitro assays. The results of the present study are in agreement with these findings.

Intake of the continuously available food during self-injection of the lower doses of these compounds was not appreciably affected. Food intake did decrease somewhat, however, when the highest doses were available. This profile contrasts previous data involving self-injection of other drugs using identical methods (Griffiths et al. 1976, 1981). Specifically, pellet intake was relatively unaffected during self-injection of a wide dose range of barbiturates or benzodiazepines, while both chlorpromazine and a series of phenylethylamine anorectics markedly suppressed food intake. The results of the present study confirm our earlier contention (Griffiths et al. 1981) that a simple relationship between the maintenance of self-injection behavior and the suppression of food intake does not exist.

In the present study, all four of the PCP analogues were found to maintain self-administration behavior at levels and response rates similar to those maintained by PCP. This finding confirms earlier reports (Shannon 1981; Cone et al. 1982) that *N*-substitutions on the PCP molecule result mainly in alterations of relative potency. The strategy used here of assessing structurally related analogues for maintenance of self-administration behavior has been used previously by this laboratory (Griffiths et al. 1976, 1981) to study various amphetamine analogues, barbiturates, and benzodiazepines. The resultant ordering of the compounds within these classes with respect to maintenance of self-administration corresponds well with the results of human drug self-administration studies, as well as the relative abuse of the various drugs (Griffiths et al. 1979a, 1980a, b). The results of the present study, therefore, suggest that PCP and the four analogues would maintain self-administration in human studies and have abuse potential.

Acknowledgements. This research was supported by National Institute on Drug Abuse contract 271-80-3718 and grant DA-01147. S. Lukas is a recipient of a NIDA National Research Service Award DA-05186. We thank B. Bailer, E. Cook, B. Giblin, D. Lattea, J. Nirenberg, and D. Weinstein for technical assistance; J. Snell for computer programming; and D. Sabotka and P. Theiss for secretarial and administrative assistance. All drugs were supplied by the National Institute on Drug Abuse.

References

Bailey K, Chow YK, Downie RH, Pike RK (1976) 1-Piperidinocyclohexanecarbonitrile, a toxic precursor of phencyclidine. J Pharm Pharmacol 28:713 – 714

Balster RL, Johanson CE, Harris RT, Schuster CR (1973) Phencyclidine self-administration in the rhesus monkey. Pharmacol Biochem Behav 1:167 – 172

Balster R. L., Woolverton W. L. (1980) Continuous-access phencyclidine self-administration by rhesus monkeys leading to physical dependence. Psychopharmacology 70:5 – 10

Carroll ME, France CP, Meisch RA (1981) Intravenous self-administration of etonitazene, cocaine and phencyclidine in rats during food deprivation and satiation. J Pharmacol Exp Ther 217:241 – 247

Carroll ME, Meisch RA (1980) Oral phencyclidine (PCP) self-administration in rhesus monkeys: Effects of feeding conditions. J Pharmacol Exp Ther 214:339 – 346

Cone EJ, Darwin WD, Yousefnejad D, Buchwald WF (1979) Separation and identification of phencyclidine precursors, metabolites and analogs by gas and thin-layer chromatography and chemical ionization-mass spectrometry. J Chromatogr 177: 149 – 153

Findley JD, Robinson WW, Gilliam W (1971) A restraint system for chronic study of the baboon. J Exp Anal Behav 15:69 – 71

Findley JD, Robinson WW, Peregrino L (1972) Addiction to secobarbital and chlordiazepoxide in the rhesus monkey by means of a self-infusion preference procedure. Psychopharmacologia 26:93 – 114

Finney DJ (1964) Statistical method in biological assay. Hafner, New York

Griffiths RR, Bigelow GE, Henningfield JE (1980a) Similarities in animal and human drug-taking behavior. In: Mello NK (ed) Advances in substance abuse: Behavioral and biological research. JAI, Greenwich, CN, pp 1 – 90

Griffiths RR, Bigelow GE, Liebson I, Kaliszak JE (1980b) Drug preference in humans: Double-blind choice comparison of pentobarbital, diazepam, and placebo. J Pharmacol Exp Ther 215:649 – 661

Griffiths RR, Bigelow GE, Liebson I (1979a) Human drug self-administration: Double-blind comparison of pentobarbital, diazepam, chlorpromazine and placebo. J Pharmacol Exp Ther 210:301 – 310

Griffiths RR, Brady JV, Bradford LD (1979b) Predicting the abuse liability of drugs with animal drug self-administration procedures: Psychomotor stimulants and hallucinogens. In: Thompson T, Dews PB (eds) Advances in behavioral pharmacology, vol 2. Academic, New York, pp 163 – 208

Griffiths RR, Lukas SE, Bradford LD, Brady JV, Snell JD (1981) Self-injection of barbiturates and benzodiazepines in baboons. Psychopharmacology 75:101–109

Griffiths RR, Winger G, Brady JV, Snell JD (1976) Comparison of behavior maintained by infusions of eight phenylethylamines in baboons. Psychopharmacology 50:251–258

Griffiths RR, Wurster RM, Brady JV (1975) Discrete-trial choice procedure: Effects of naloxone and methadone on choice between food and heroin. Pharmacol Rev 27:357–365

Hampton RY, Medzihradsky F, Woods JH, Dahlstrom PJ (1982) Stereospecific binding of ^{3}H-phencyclidine in brain membranes. Life Sci 30:2147–2154

Jasinski DR, Cone EJ, Gorodetzky CW, Risner ME, Shannon HE, Su TP, Vaupel DB (1979) Progress report from the NIDA Addiction Research Center. Nat Inst Drug Abuse Res Monogr 27:61–69

Jasinski DR, Shannon HE, Cone EJ, Vaupel DB, Risner ME, McQuinn RL, Su, TP, Pickworth WB (1981) Interdisciplinary studies on phencyclidine. In: Domino EF (ed) PCP: Historical and current perspectives. NNP Books, Ann Arbor MI, pp 331–400

Johanson CE, Balster RL (1978) A summary of the results of self-administration studies using substitution procedures in primates. Bull Narc 30:43–54

Kalir A, Edery H, Pelah Z, Balderman D, Porath G (1969) 1-Phenylcycloalkylamine derivatives. II. Synthesis and pharmacological activity. J Med Chem 12:473–477

Kalir A, Maayani S, Rehavi M, Elkavets R, Pri-Bar I, Buchman, O, Sokolovsky, M. (1978) Structure-activity relationship of some phencyclidine derivatives: In vivo studies in mice. Eur J Med Chem 13:17–24

Lukas SE (1983) Subcutaneous splicing of intravenous and intragastric catheters. Pharmacol Biochem Behav 18:267–268

Lukas SE, Griffiths RR, Bradford LD, Brady JV, Daley L, Delorenzo R, (1982) A tethering system for intravenous and intragastric drug administration in the baboon. Pharmacol Biochem Behav 17:823–829

McCarthy DA, Harrigan SE (1977) Dependence-producing capacity of ketamine in the *Macaca mulatta*. In: Hulsz E, Sanchez-Hernandez JA, Vasconcelos G, Lunn JN (eds) Anaesthesiology: Proceedings of the Sixth World Congress of Anaesthesiology. Excerpta Medica, Amsterdam, pp 160–168

Moreton JE, Meisch RA, Stark L, Thompson T (1977) Ketamine self-administration by the rhesus monkey. J Pharmacol Exp Ther 203:303–309

Pickens R, Thompson T, Muchow, DC (1973) Cannabis and phencyclidine self-administration by animals. In: Goldberg L, Hoffmeister F, (eds) Psychic dependence: Bayer-Symposium IV. Springer, Berlin Heidelberg New York, pp 78–86

Risner ME (1982) Intravenous self-administration of phencyclidine and related compounds in the dog. J Pharmacol Exp Ther 221:637–644

Shannon HE (1981) Evaluation of phencyclidine analogs on the basis of their discriminative stimulus properties in the rat. J Pharmacol Exp Ther 216:543–551

Shulgin AT, MacLean DE (1976) Illicit Synthesis of phencyclidine (PCP) and several of its analogs. Clin Toxicol 9:553–560

Smialek JE, Monforte JR, Gault R, Spitz WU (1979) Cyclohexamine (rocket fuel): Phencyclidine's potent analog. J Anal Toxicol 3:209–212

Vincent JP, Kortalovski B, Geneste P, Kaminka JM, Lazdunski M (1979) Interaction of phencyclidine (angel dust) with a specific receptor in rat brain membranes. Proc Natl Acad Sci USA 76:4678–4682

Received April 28, 1983; Final version January 31, 1984