0022-3565/02/3012-690–697$7.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 301, No. 2
4629/981651
Printed in U.S.A.

JPET 301:690–697, 2002

Relative Reinforcing Strength of Three *N*-Methyl-D-Aspartate Antagonists with Different Onsets of Action

G. WINGER, S. R. HURSH, K. L. CASEY, and J. H. WOODS

Departments of Pharmacology and Psychology (G.W., J.H.W.) and Physiology and Neurology (K.L.C.), University of Michigan, Ann Arbor, Michigan; Science Applications International (S.R.H.), Joppa, Maryland; and Johns Hopkins University School of Medicine (S.R.H.), Baltimore, Maryland

Received October 9, 2001; accepted February 6, 2002 This article is available online at http://jpet.aspetjournals.org

ABSTRACT

The potential contribution of onset and duration of pharmacological action to the reinforcing strength of three intravenously delivered *N*-methyl-D-aspartate antagonists was evaluated in this study. The onsets and durations of action of ketamine, phencyclidine, and dizocilpine were evaluated by observation and tabulation of their behavioral effects in rhesus monkeys after i.v. administration. The reinforcing effects of each drug were tested in a paradigm in which the fixed ratio requirements for i.v. drug injection were increased systematically. The peak observable effect of ketamine occurred immediately after its administration. There were some immediately observable effects of phencyclidine, although the peak effect of phencyclidine was delayed for 3 to 10 min. Dizocilpine had few immediate effects and a peak effect 32 min after administration. Ketamine had the shortest duration of action, followed by phencyclidine and dizocilpine. Analysis of demand curves and response output curves that were normalized to account for potency differences among the drugs revealed that ketamine and phencyclidine were equally effective as reinforcers, and they were both much stronger reinforcers than was dizocilpine. The data therefore suggest that a fast onset of action increases the reinforcing strength of drugs, although duration of action may play a role as well.

It is generally reported that stimuli function better as reinforcers (i.e., maintain higher response rates) if there is little to no delay between the response that produces them and their delivery (Renner, 1964; de Villiers, 1977). This has been shown as well in situations in which drugs serve as reinforcers. Imposing a delay between a response and drug administration reduced the rates of behavior maintained by intravenous cocaine and procaine (Beardsley and Balster, 1993), and cocaine maintained lower rates of responding when it was delivered slowly (Balster and Schuster, 1973; Panlilio et al., 1998). Studies in humans indicated that a single oral dose and divided oral doses of diazepam or pentobarbital produced similar peak plasma drug levels, but these levels were reached more quickly after the single dose. Measures of drug-induced euphoria were significantly higher after administration of the single dose (de Wit et al., 1992, 1993). Recently, Abreu et al. (2001) reported that rapid infusions (30 mg/70 kg over 2 s) of cocaine produced greater subjective effects than slower (60-s) injections of the same dose, whereas subjects did not respond differentially to rapid versus slow infusions of 3 mg/70 kg hydromorphone. Marsch et al. (2001) evaluated the effects of rate of intravenous morphine infusion (5 and 10 mg/70 kg) on physiological and subjective responses to the drug in normal volunteers. They found that faster infusions (2 min) produced higher peak plasma levels of morphine and greater positive subjective reports than slower infusions (60 min).

Most of these studies support the notion that greater effects, including subjective and reinforcing effects, accompany rapid drug administration. It should be true as well that drugs with more rapid onsets of action are stronger reinforcers than drugs with similar pharmacological effects but slower onsets of action.

Phencyclidine, ketamine, and dizocilpine are structurally diverse compounds that have many common pharmacological effects; these appear to be mediated by uncompetitive antagonism of the effects of glutamate at the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors (Anis et al., 1983; Mendelson et al., 1984; Koek and Woods, 1988a). Two of the several effects that NMDA antagonists may have in common in rhesus monkeys are their ability to produce characteristic behavioral impairment resulting in dissociative anesthesia (Chen and Weston, 1960), and their ability to serve as reinforcing stimuli (Balster et al., 1973; Moreton et al., 1979; Winger et al., 1991). Koek and Woods (1988b) noted that the uncompetitive NMDA antagonists ketamine, phencyclidine, and dizocilpine, as well as dexoxadrol and (+)-*N*-allyl-

This research was supported by U.S. Public Health Service Grant DA-09161.

ABBREVIATIONS: NMDA, *N*-methyl-D-aspartate; MK-801, (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine maleate.

normetazocine, produced a very similar and pharmacologically specific anesthesia in rhesus monkeys. The maintenance of both respiratory rate and muscle tone in the presence of anesthesia was characteristic of these drugs. The reinforcing effects of phencyclidine and phencyclidine-like drugs have been observed in rats, dogs, and baboons, as well as in rhesus monkeys (Young and Woods, 1981; Slifer and Balster, 1983; Lukas et al., 1984; Marquis et al., 1989). In an early study, phencyclidine did not maintain behavior well in rhesus monkeys when the fixed ratio was increased from 1 to 5 (Balster et al., 1973). Ketamine, however, maintained behavior as the fixed ratio was increased (Moreton et al., 1979). This suggested the possibility that these two compounds were quite different in their reinforcing strengths. Dizocilpine maintained behavior in the majority of monkeys when it was substituted for ketamine (Koek et al., 1988; Beardsley et al., 1990), although in some situations, rates of responding maintained by dizocilpine were lower than those maintained by phencyclidine or ketamine (Winger et al., 1989, 1991).

In the present study, the speed of onset and duration of action of observable behavioral effects of three NMDA antagonists were determined after their intravenous administration to rhesus monkeys. In addition, the ability of these drugs to maintain responding in a situation in which the behavioral output required for drug delivery was increased periodically was assessed and analyzed using traditional rate measures as well as procedures that allowed comparisons among the drugs with respect to their reinforcing strength (Hursh and Winger, 1995).

Materials and Methods

Overt Behavioral Effects and Anesthesia

Subjects and Apparatus. Three adult rhesus monkeys, two males and one female, were observed after i.v. administration of each of the three NMDA antagonists. Each of the subjects had a history of self-administration of these drugs, although they were not used in the self-administration study reported herein. The monkeys were housed individually in stainless steel cages measuring 83.3 × 76.2 × 91.4 cm. Silicone rubber (Mox-Med, Portage, WI) catheters had been surgically implanted in a jugular, femoral, external jugular, or brachial vein of each monkey. Surgery was performed under aseptic conditions using 10 mg/kg ketamine and 2 mg/kg xylazine as anesthetics. After surgery, the monkeys wore tubular stainless steel harnesses that protected the catheters that passed subcutaneously from the surgical incision site to the midscapular exit sites. The harnesses were attached to flexible tethers that carried the catheters to the outside rear of the cages. The research reported herein has been conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

Procedure. At least two doses of each of the three NMDA antagonists were administered to each of the three monkeys. The selected dose of drug was administered through the indwelling catheter, which was then flushed with approximately 3 ml of sterile saline. At the time the flush was completed, a clock was started, and the monkeys were observed at 1, 3, 10, 32, 56, 100, 178, and 320 min. Observations were discontinued when the monkeys no longer showed any effects of the administered drugs.

The animals' behavior was scored on a sheet like that shown in Table 1. The items on the sheet were developed by observing and rating several monkeys that had been given relatively large doses of ketamine intravenously. The three items reflecting reaction to the environment and the miscellaneous items of salivation and nystagmus were rated simply as present (+1) or absent (0). The postural changes were weighted and scored from 0 to +6. The + scores were added for each time of observation to yield a total score for that animal. The maximum score that could be attained was 11. Scores of 10 or 11 reflected a monkey that was unresponsive to touch or pin prick, that was lying down, and that showed no resistance to passive movement (i.e., anesthesia). For the initial three or four observations of the effects of ketamine, the monkeys were rated by two observers who were aware of the drug being administered but scored the animals independently. The observers subsequently compared notes to ensure that they were responding to the monkeys with similar scores. Further evaluation was continued with only one of the observers, who was blind to the drug being administered. The observer stood in front of the monkeys' cages during the observation period.

TABLE 1
Check list for recording the behavioral effects of NMDA antagonist administration

Reaction to environment
Unable to follow with head or eyes
Unreactive to touch
Unreactive to pinprick
Posture
+6 No passive movement; flaccid
+5 Does not maintain posture; resists passive movement?
+4 Does not maintain posture but holds head up
+3 Sitting up but no spontaneous movement
+2 Moves spontaneously, but poor coordination and poor fine-motor control
+1 Well coordinated, but poor fine motor control
0 Moves in coordinated manner, good fine motor control
Miscellaneous
Salivation
Nystagmus

Self-Administration

Subjects and Apparatus. Three adult male monkeys served as subjects in this phase of the study. They were housed individually in the same types of cages as those described above for the observation studies. The cages each had a response panel mounted on the side that contained three stimulus lights over two response levers. The two outside lights could be illuminated red; the center light could be illuminated green and was yoked to the infusion pump. The monkeys had indwelling i.v. catheters implanted as described above and wore Teflon mesh jackets (Lomir Biomedical, Malone, NY) to protect the catheters. These jackets attached to flexible tethers that carried the catheters to the outside rear of the cages where they connected to infusion pumps (model MHRK 55; Watson-Marlow Co., Falmouth, UK).

Procedure. Sessions of drug availability lasted for 130 min and occurred twice daily, at 10:00 AM and 4:00 PM. Drug availability was signaled by the illumination of one of the two red stimulus lights. In the presence of the red light, after the specified number of lever-press responses, the red light was turned off, the pump was operated for 5 s, 1 ml of drug or saline solution was delivered, and the green, center light was illuminated. Pump operation was followed by 10 s of time-out in which no lights were illuminated in the cage and lever-press responses had no scheduled consequence.

Three doses of each of the three NMDA antagonists were evaluated in the self-administration studies. Typically, a given dose was made available to the monkeys at the smallest fixed ratio value (fixed ratio 1) for five to seven sessions. Once consecutive sessions of drug availability had been studied, saline was made available for several consecutive sessions at the same ratio. The fixed ratio then was increased to 10, and this dose was available for another five sessions followed by saline availability. In a similar manner, fixed ratios of 32, 100, 320, and 1000 were tested, each for five to seven sessions at each dose. The dose of drug was then changed, typically

increased, and this procedure repeated for the three doses of each compound.

The five to seven sessions during which each dose was available at a given fixed ratio value were consecutive sessions for all doses of ketamine. Ketamine is sufficiently short-lasting that each session was independent of the previous session; behavior was similar during the morning sessions that started 16 h after the previous self-administration opportunity and the evening sessions, 4 h since drug was last available. For phencyclidine and dizocilpine, which had longer durations of action, drug was typically available on only one of the two daily sessions, either in the morning or in the afternoon, and saline, at the same fixed ratio, was available in the other session. This was done to ensure independent measures for these longer acting drugs. When ratios increased to the point where only one or two injections of dizocilpine or phencyclidine were taken in a session, drug was made available on consecutive sessions. Due to an oversight, two of the monkeys did not receive the largest dose of dizocilpine at a fixed ratio 1. The data were analyzed using information from the single monkey who received this dose at this ratio.

Drugs

Dizocilpine (MK-801; Sigma-Aldrich, St. Louis, MO) and phencyclidine hydrochloride (National Institute on Drug Abuse, Rockville, MD) were dissolved in physiological saline. These drugs were made up in concentrations of between 1 and 10 mg/ml for intravenous administration in the studies of direct observation. Ketamine hydrochloride (Vetpo, Holland, MI) was used as the commercially available solution of 100 mg/ml with 0.1 mg/ml benzethonium chloride added as a preservative.

Data Analysis

Overt Behavioral Effects and Anesthesia. Total impairment scores were recorded for each monkey for each time by adding the number of + scores recorded on the observation chart. These were plotted for the individual animals as impairment scores over time for each of two doses of each drug.

Self-Administration. Rates of responding were calculated as the number of responses made during illumination of the red stimulus light, divided by the number of seconds the light was illuminated in each 130-min session. Drug intake was calculated as the dose in milligrams per kilogram per injection multiplied by the number of injections taken in each session. These values were averaged over the last five sessions at each fixed ratio value for each monkey. Occasionally, equipment failure limited to four the number of sessions of exposure to a particular dose for a particular monkey, in which case, these four sessions were averaged for this animal. The rate and intake values were then averaged across the three monkeys to provide the data for the figures.

Normalized demand curves were constructed using the procedure described by Hursh and Winger (1995). Normalization was necessary because demand curves contain milligrams of drug in both the ordinate (consumption of drug in mg/kg/session) and the abscissae (price as ratio/reinforcer in mg/kg/injection). Thus, before normalization, the demand curves were strongly influenced by the potency of the drugs, which varied widely in these three compounds. Normalization effectively set the consumption of each drug to the same value (log 100) at the smallest price (fixed ratio 1 at the largest dose). The effect of increases in price on drug consumption starting at this normalized value was then compared for each drug.

Data for the smallest dose of dizocilpine were not included in these analyses because, as shown below, this dose did not yield rates of responding indicative of reinforcing effects. Likewise, data for fixed ratio 1000 are also omitted from the analyses; not all animals received the fixed ratio 1000 condition, and frequently no drug injections were obtained at this fixed ratio in the animals who did receive it. The values of normalized dose (q) (100/consumption at the lowest fixed ratio), normalized price (P) (fixed ratio/q), and normalized consumption (Q) (number of reinforcers per session at each fixed ratio $\cdot$ q), as well as log P and log Q were calculated in an Excel spreadsheet. This information was graphed in GraphPad Prism (GraphPad Software, San Diego, CA) using nonlinear curve fitting and the formula $Y = \log(100) + B(X) - (A \cdot (10 \wedge X)) \cdot \log(e)$, where Y is log Q and X is log P. Initial values were set to $b = -0.05$ and $a = 0.004$. GraphPad Prism returned values for initial slope (b), acceleration (a), and variance accounted for by the curve fit (R^2). These were returned to the Excel spreadsheet, where elasticity of the demand functions (P_{max}) and O_{max} were calculated.

Normalized response output functions were calculated using a similar procedure. The formula for response output functions was $Y = \log(100) + ((B + 1)(X)) - (A \cdot (10 \wedge X)) \cdot \log(e)$, where Y is log responses and X is log P. Initial values were the same as those for the calculation of demand functions. A repeated measures analysis of variance was used to determine differences among the P_{max} and O_{max} data.

Results

Overt Behavioral Effects and Anesthesia. Total impairment scores for two doses of ketamine, phencyclidine, and dizocilpine are shown for individual monkeys over time in Fig. 1. Each of the three drugs produced a maximum or near maximum score of 10 or 11 after i.v. administration of the larger of two doses. The peak effect of 10 mg/kg ketamine occurred as quickly as the observations could be made after intravenous administration. A dose of 3.2 mg/kg also had its peak effect at the first observation time of 1 min, but this effect was considerably less profound than was that produced by 10 mg/kg. Virtually all observable effects of 3.2 mg/kg ketamine had disappeared at 32 min after administration, and all directly observable effects of 10 mg/kg ketamine had disappeared at the 100-min observation point.

Phencyclidine's overall effects indicated a variable but clear effect of both doses within 1 min after i.v. administration and a rapidly increasing effect over the next 2 min. This effect was maintained, or increased if it was not maximal, at 10 min, and then decreased gradually to complete recovery by 100 to 178 min. One monkey showed a more gradual increase in effects, reaching a peak effect at 32 min rather than at 3 or 10 min as with the two other monkeys. The effects of the smaller dose of 1.0 mg/kg were only slightly less than those of the larger dose of 1.8 mg/kg; the smaller dose did not produce quite as high a maximum response, and, in two of the three monkeys, the effects of the smaller dose did not last as long as did those of the larger dose.

Dizocilpine at doses of 0.1 and 0.32 mg/kg, given i.v., had very little effect at the first observation time of 1 min. The effects of the larger dose increased gradually and reached a peak effect, which included prostration and lack of responsiveness to pinprick, 32 min after administration. The effects of the smaller dose also increased gradually and peaked at 32 min after administration, but this peak effect was considerably less than that produced by the larger dose. The duration of effect of the smaller dose of 0.1 mg/kg was 178 min, whereas the effects of the dose of 0.32 mg/kg had disappeared at the 320-min measurement time.

Self-Administration. Rates of responding and the corresponding drug intake for the three NMDA antagonists is shown in Fig. 2. Rates of saline-maintained responding are not shown, but they tended to increase as the ratio increased, peaked at a ratio value of 32 or 100, and were never greater

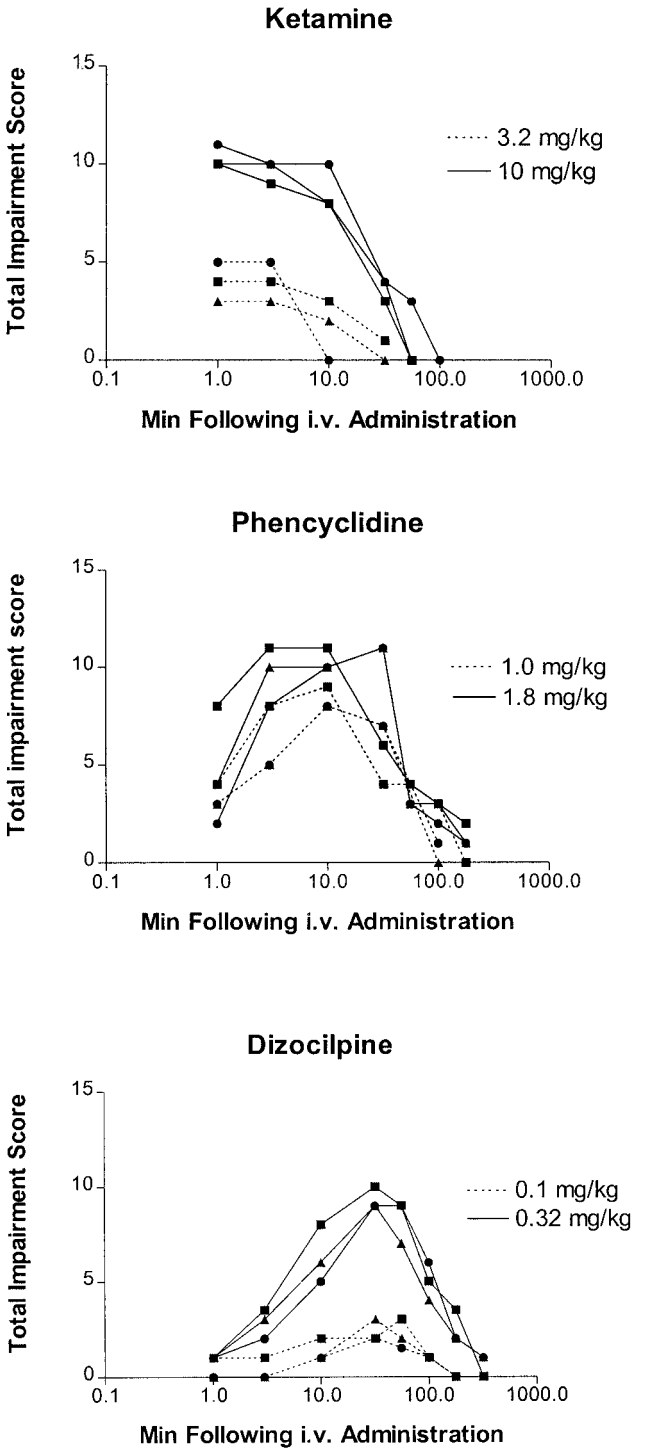

Fig. 1. Effects of intravenous administration of two doses of ketamine (top), phencyclidine (middle), and dizocilpine (bottom) on directly observable behavior of three rhesus monkeys over time. Abscissae: time in minutes on a log scale. Ordinates: total impairment scores as counted by observers using the scoring sheet shown in Table 1. The different symbols indicate effects in individual monkeys. The effects of the smaller dose of each drug are connected by dashed lines, and the effects of the larger dose are connected by solid lines.

than 0.17 responses/s under any condition. As shown in Fig. 2, left, each of the three drugs maintained rates and patterns of responding that indicated that they served as reinforcers. This was true of each of the three doses of ketamine and phencyclidine, but was true only of the two larger doses of dizocilpine. Two of the three monkeys showed similar rates of responding across the drug, dose, and fixed ratio conditions; the third monkey had consistently lower rates of responding across all drugs, and did not demonstrate rates of responding above those maintained by saline with any dose of dizocilpine. For ketamine and phencyclidine, this monkey typically showed peak levels of responding at the same fixed ratio values as the other two monkeys. These rates were simply lower for this animal.

The most rapid peak rates of responding were maintained by ketamine, followed by phencyclidine. Dizocilpine maintained the slowest peak rates of responding. The overall pattern of the effects of increasing fixed ratio value on rates of responding was an inverted U shape. Thus, rates of responding were slow at the small fixed ratios, increased to a maximum as fixed ratio increased, and declined with further increases in fixed ratio. In addition, there was a rightward shift in the fixed ratio-response curve as dose was increased. As fixed ratio was increased, there was a consistent dose-related pattern of rates of responding: on the ascending limb of the fixed ratio curves, the smaller the dose, the higher were the rates of responding. On the descending limb of the fixed ratio curves, the larger doses maintained higher rates than the smaller doses.

Drug intake is shown in Fig. 2, right. Greatest drug intakes were shown when the largest doses were available for self-administration, and intake decreased monotonically as fixed ratio increased. Thus, the highest intakes occurred at the largest dose and smallest fixed ratio. These intakes were 0.16 mg/kg dizocilpine, 1.98 mg/kg phencyclidine, and 26 mg/kg ketamine.

In Fig. 3, the demand and response output curves for the three drugs are graphed. Both the demand and response output curves generated by ketamine and phencyclidine were virtually overlapping, whereas the dizocilpine curve was located to the left and down from the ketamine and phencyclidine curves. This indicates that the dizocilpine demand curve was more elastic and the maximum response output was less than were those of ketamine and phencyclidine, which suggests in turn that dizocilpine was a less strong reinforcer than were the other two drugs.

The demand curves for each drug resulted in P_{max} and O_{max} values that could be compared. Table 2 shows the values for each drug as well as the goodness of fit (R^2) value for each demand function. The goodness of fit for the demand curves to the obtained data was excellent; values of greater than 0.97 were shown by each of the drugs. The O_{max} for ketamine was slightly larger than that for phencyclidine, but not statistically significant ($F = 0.73$, $P = 0.5$), whereas the O_{max} for dizocilpine was significantly smaller ($F = 17.28$, $P = 0.05$). The P_{max} values, like the O_{max} values, were not significantly different for ketamine (316) and phencyclidine (232) ($F = 0.27$, $P = 0.6$), but values for both of these drugs were significantly larger than the P_{max} for dizocilpine ($F = 19.45$, $P = 0.05$). The order of both P_{max} and O_{max} values was ketamine > phencyclidine ≫ dizocilpine.

Discussion

Ketamine, phencyclidine, and dizocilpine are NMDA antagonists with similar behavioral and pharmacological ef-

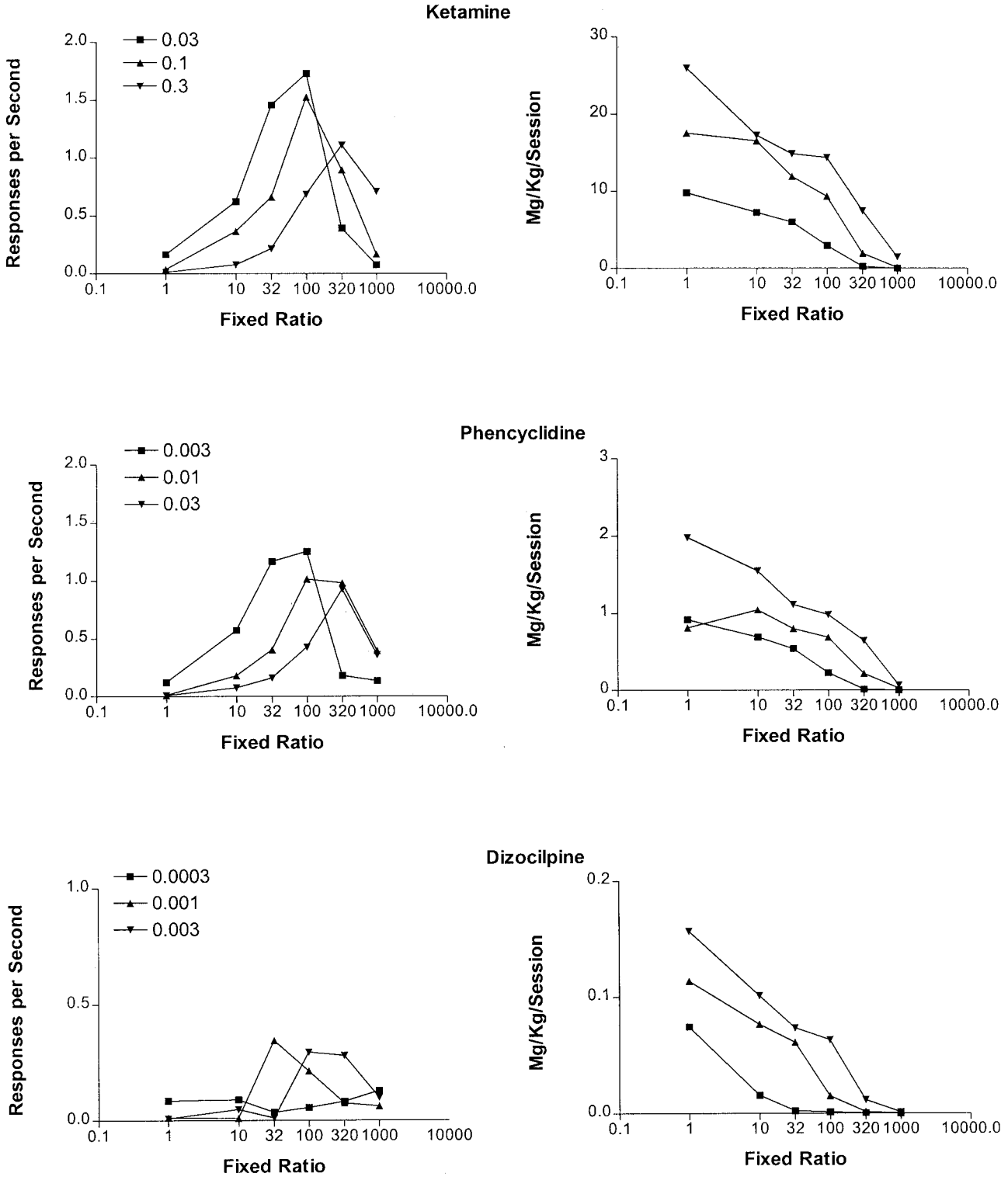

Fig. 2. Rates of drug-contingent responding (left) and total drug intake (right) across increasing fixed ratios in rhesus monkeys with one of three doses of ketamine (top), phencyclidine (middle), and dizocilpine (bottom) available for i.v. self-administration. Abscissae: fixed ratio values for response-contingent drug administration. Ordinates (left): rates of responding in responses per second. Note the different ordinate scale for dizocilpine. Ordinates (right): total session intake of each drug in milligrams per kilogram. The smallest dose/injection of each drug is designated by squares, the intermediate dose by triangles, and the largest dose by inverted triangles.

fects. Their primary differences lie in their potencies, onsets, and durations of action: ketamine is the least potent with the fastest onset and shortest duration; phencyclidine has an intermediate potency, rate of onset, and duration of action; and dizocilpine is the most potent of the three drugs, with a relatively slow onset of action and a relatively long duration of action. These difference and similarities were observed after intravenous administration of these three drugs. Each

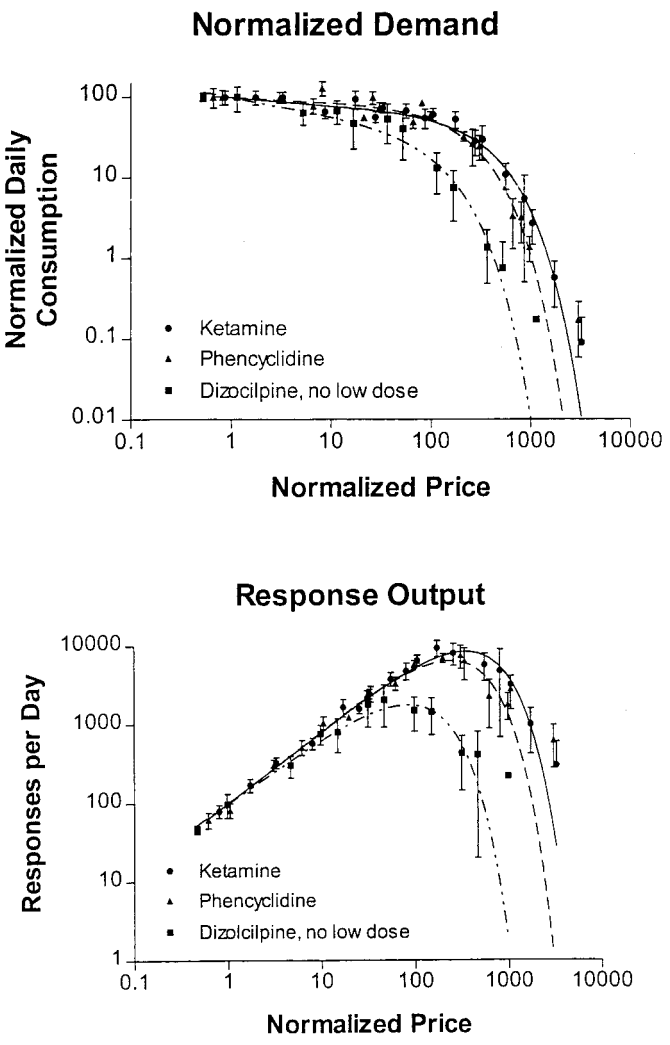

Fig. 3. Demand curves (top) and response-output demand curves (bottom) generated by ketamine (●), phencyclidine (▲), and dizocilpine (■). Abscissae: log price (fixed ratio/dose) normalized to account for potency difference. Ordinate, top: log of session drug consumption, normalized to account for potency differences among the drugs. Ordinate, bottom, log of responses per session.

TABLE 2

Goodness of fit of data to the demand function (R^2), P_{max}, and area under the demand curve results for each of the three NMDA antagonists

Drug	R^2	P_{max}	O_{max}
Ketamine	0.98	316	8790
Phencyclidine	0.97	231	7261
Dizocilpine	0.98	89	1930

produced dose-related, profound, and similar observable behavioral effects, culminating in prostration and lack of response to environmental manipulation. Ketamine produced its strongest observable effects following administration of 3.2 mg/kg, and these were observed immediately after drug administration. All effects of this dose of ketamine had disappeared at 32 or 100 min. Phencyclidine also had immediate effects after administration of 1.0 and 1.8 mg/kg, but these effects became more marked over the first 3 min. Effects of the larger dose of phencyclidine were still present in mild form 178 min after administration. Dizocilpine had more slowly developing effects after administration of the most effective dose of 0.32 mg/kg. Very little effect was observed immediately; effects were clearly present at 3 min, and peak effects of 0.32 mg/kg dizocilpine were delayed until 32 min after drug administration. Two animals continued to show some effects of dizocilpine 320 min after administration. Thus, the similarity of pharmacological action, with differences in potency, onset, and duration of action were confirmed in this study. The observable effects of these drugs have been described in detail by Koek and Woods (1988b) and include nystagmus, ataxia, and anesthesia without loss of muscle tone or eye closure. Similar effects were observed in the present study.

Each of the three NMDA antagonists functioned as a reinforcer. The ability of each of these drugs to maintain behavior on which its i.v. administration was contingent has been shown by several other investigators using rhesus monkeys as subjects (Balster et al., 1973; Moreton et al., 1979; Young and Woods, 1981; Koek et al., 1988; Winger et al., 1989; Beardsley et al., 1990). These drugs had similar differences in potency in the self-administration studies as they had shown in direct behavioral observation studies, both in terms of the doses that maintained maximum rates of responding and in terms of total drug intake. Rates of responding as a function of fixed ratio showed a pattern that has been demonstrated with drugs from other pharmacological classes (Lemaire and Meisch, 1985; Winger, 1993). Low rates of responding were shown at low fixed ratio values, and these rates increased with increasing fixed ratio values until a peak was reached. As ratios increased above this value, rates declined again. The low rates occurring with low fixed ratio values have been observed in situations where reinforcers other than drug are available (Hursh, 1984; Hursh et al., 1988; Bauman et al., 1996). These low rates may be due primarily to the rate-decreasing effects of accumulated reinforcers (e.g., satiation). This is supported by the fact that, even at low fixed ratios, rates were higher when smaller doses of drug were response-contingent. Interestingly, at the smallest fixed ratio value, in the 130-min sessions, monkeys self-administered 2.5 times the dose of ketamine that, when given as a bolus, produced a total impairment score of 10. The session intake of phencyclidine was equal to the bolus dose that produced a total impairment score of 10, and the session intake of dizocilpine was half the bolus amount that produced a total impairment score of 10. This difference in drug intake as a proportion of the amount of drug producing anesthesia probably reflects a difference in the duration of action of the drugs, which impacts the amount that can be self-administered in a 2-hour session. Nevertheless, it is perhaps noteworthy that dizocilpine did not maintain high rates of responding even though the amount self-administered was less than that producing anesthesia. Presumably, the inability of dizocilpine to produce high rates of responding at intermediate fixed ratio values was not due to the direct behaviorally impairing effects of the drug but rather to its weak reinforcing effectiveness.

As increasing fixed ratios led to reductions in drug intake, rates of responding increased. The maximum rate tended to occur at lower ratios for smaller doses, reflecting, most likely, the reduced ability of small doses to maintain behavior when the ratio was large. Thus, at the largest ratio or ratios, rates of responding decreased more precipitously for the smaller

doses. This may indicate a lower reinforcing strength of smaller doses of each of these drugs.

Collapsing doses and ratios into a single price measure (ratio/dose) removed the differential effect of dose on response rates, and allowed a single response-output demand function to be drawn. As indicated by Bickel et al. (1995), the fact that a single demand function could be used to describe the interaction of response output or consumption and the independent variables of ratio and dose, indicates that increasing the ratio is behaviorally identical to decreasing the dose of drug. The comparative demand and response-output functions were obtained using a normalization procedure that corrected for the differences in potencies among the drugs, and the differences in reinforcing strength could be more clearly observed. Two measures, P_{max} and O_{max}, were compared. P_{max} is the price at which peak response output occurs, and is also the point at which elasticity of the demand curve is equal to -1. Larger P_{max} values indicate a less elastic demand function, with drug consumption declining at relatively higher prices. Therefore, larger P_{max} values indicate a more reinforcing drug. O_{max} incorporates level of demand as well as elasticity. Larger O_{max} values indicate that a drug is maintaining more total responses. Higher O_{max} values also indicate a more reinforcing drug. In previous studies using four drugs, P_{max} values were not consistently ordered the same as O_{max} values (Hursh and Winger, 1995). In the current study, both measures yielded the same ordering of drugs: ketamine and phencyclidine were nearly equally strong as reinforcers with statistically similar P_{max} and O_{max} values. Both of these drugs were stronger reinforcers than was dizocilpine, which had smaller P_{max} and O_{max} values.

The relation between P_{max} and O_{max} is not yet understood. Bickel et al. (2000) theorizes that reinforcement effectiveness is not a unitary concept, but a heterogenous one. It is indicated by, among other things, elasticity or P_{max}, which is correlated with the amount of effort an animal is willing to expend to earn the reinforcer (e.g., break point on a progressive ratio measure), and O_{max}, the response output at P_{max}, which is correlated with how much the animal responds to earn the reinforcer. There are data that indicate that P_{max} and O_{max} do not covary (Hursh and Winger, 1995; Bickel et al., 2000), but it is not intuitively obvious why they do not. Neither is it obvious whether one is a more appropriate measure of reinforcing effectiveness than the other; whether both are helpful, important, or necessary; or how they relate to each other. This information is likely to come as more data are gathered, and more discussion encouraged on these concepts.

The differences in the reinforcing effectiveness of these drugs could be due, among other possible factors, to pharmacological distinctions among them, to differences in their durations of action, or to differences in their onsets of action. Pharmacological distinctions among these drugs are much less commonly reported in the literature than are pharmacological similarities. There is evidence that phencyclidine is superior to ketamine and dizocilpine as a dopamine reuptake blocker (Johnson and Jones, 1990), but this does not explain the fact that phencyclidine and ketamine functioned equally well as reinforcers. In addition, the rank order potency of most of the drugs' actions at the NMDA receptor are the same as their rank order potency in behavioral and physiological measures (Parsons et al., 1995), supporting the notion that it is the action at this receptor that is responsible for the reinforcing effects of these drugs.

The marked differences in duration of action of these three compounds could also contribute to the differences in the ability of these drugs to maintain behavior. Drug accumulation should be greater with drugs with long durations of action, and this could lead to suppression of behavior. The use of the increasing fixed ratio procedure helps to mitigate the potentially suppressing effects of long-acting compounds. As the ratio increases, the time between drug administration increases as well. For a drug that functions well as a reinforcer, even with a long duration of action, behavior should be maintained as the fixed ratio value and the time between injections increases. This is most clearly seen with ketamine and phencyclidine, which differ considerably in their durations of action; they were nearly equally effective as reinforcers. Furthermore, opioids that differed considerably, and apparently exclusively, in their durations of action did not differ in their relative reinforcing effects (Ko et al., 2002). It is therefore our conclusion that difference in duration of action is relatively unimportant in influencing the reinforcing effectiveness. Speed of onset seems to be the most important distinction among these drugs in this situation and, all other things being equal, drugs with rapid onsets of action serve better as reinforcers than drugs with slow onsets of action.

Although there is not a one-to-one correspondence between effectiveness of a drug as a reinforcer in the laboratory, and abuse liability of the drug "on the street", it is likely that speed of onset of drug action impacts drug abuse directly. Not only drugs with rapid onsets of action but also routes of administration that produce more rapid effects (i.v. versus s.c.; smoking versus insufflation) are likely to lead to greater involvement of the individual with the drug. This aspect of drug action is therefore a critical one in attempts to understand factors that contribute to the abuse of a particular drug.

Acknowledgments

We appreciate the careful technical assistance of Laurie Heller and Debbie Huntzinger. We also thank Jef Vivian for setting up the Excel spreadsheets for calculation of P, Q, $\log P$, $\log Q$, P_{max}, R^2, and O_{max} values.

References

Abreu ME, Bigelow GE, Fleisher L, and Walsh SL (2001) Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. *Psychopharmacologia* **154:**76–84.

Anis NA, Berry SC, Burton NR, and Lodge D (1983) The dissociative anesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurons by *N*-methyl-aspartate. *Br J Pharmacol* **79:**565–575.

Balster RL, Johanson C-E, Harris L, and Schuster CR (1973) Phencyclidine self-administration in the rhesus monkey. *Pharmacol Biochem Behav* **1:**169–172.

Balster RL and Schuster CR (1973) Fixed-interval schedule of cocaine reinforcement: effect of dose and infusion duration. *J Exp Anal Behav* **20:**119–129.

Bauman RA, Raslear TG, Hursh SR, Shurtleff D, and Simmons L (1996) Substitution and caloric regulation in a closed economy. *J Exp Anal Behav* **65:**401–422.

Beardsley PM and Balster RL (1993) The effects of delay of reinforcement and dose on the self-administration of cocaine and procaine in rhesus monkeys. *Drug Alcohol Depend* **34:**37–43.

Beardsley PM, Hayes BA, and Balster RL (1990) The self-administration of MK-801 can depend upon drug-reinforcement history, and its discriminative stimulus properties are phencyclidine-like in rhesus monkeys. *J Pharmacol Exp Ther* **252:** 953–959.

Bickel WK, DeGrandpre RJ, and Higgins ST (1995) The behavioral economics of concurrent drug reinforcers: a review and re-analysis of drug self-administration research. *Psychopharmacology* **118:**250–259.

Bickel WK, Marsch LA, and Carroll ME (2000) Deconstructing relative reinforcing efficacy and situating the measures of pharmacological reinforcement with behavioral economics: a theoretical proposal. *Psychopharmacology* **153:**44–56.

Chen GM and Weston JK (1960) The analgesic and anesthetic effects of 1-(1-phencyclohexyl) piperidine HCl on the monkey. *Anesth Analg* **34:**132–137.
de Villiers P (1977) Choice in concurrent schedules and a quantitative formulation of the law of effect, in *Handbook of Operant Behavior* (Honig WK and Staddon JER eds) pp 233–287, Prentice-Hall, Englewood Cliffs, NJ.
de Wit H, Bodker B, and Ambre J (1992) Rate of increase of plasma drug level influences subjective response in humans. *Psychopharmacology* **107:**352–358.
de Wit H, Dudish S, and Ambre J (1993) Subjective and behavioral effects of diazepam depend on its rate of onset. *Psychopharmacology* **112:**324–330.
Hursh SR (1984) Behavioral economics. *J Exp Anal Behav* **42:**435–452.
Hursh SR, Raslear TG, Shurtleff D, Bauman R, and Simmons L (1988) A cost-benefit analysis of demand for food. *J Exp Anal Behav* **50:**419–440.
Hursh SR and Winger G (1995) Normalized demand for drugs and other reinforcers. *J Exp Anal Behav* **64:**373–384.
Johnson KM and Jones SM (1990) Neuropharmacology of phencyclidine: basic mechanisms and therapeutic potential. *Annu Rev Pharmacol Toxicol* **30:**707–750.
Ko MC, Terner J, Hursh S, Woods JH, and Winger G (2002) Relative reinforcing effects of three opioids with different durations of action. *J Pharmacol Exp Ther* **301:**698–704.
Koek W and Woods JH (1988a) Correlations between phencyclidine-like activity and *N*-methyl-D-aspartate antagonism: behavioral evidence, in *Sigma and Phencyclidine-like Compounds as Molecular Probes in Biology* (Domino EF and Kamenka JM eds) pp 357–372, NPP Books, Ann Arbor, MI.
Koek W and Woods JH (1988b) Assessing directly observable behavioral-like effects of phencyclidine (PCP)-like drugs in pigeons, in rats, and in rhesus monkeys, in *Sigma and Phencyclidine-like Compounds as Molecular Probes in Biology* (Domino EF and Kamenka J-M) pp 493–509, NPP Books, Ann Arbor, MI.
Koek W, Woods JH, and Winger G (1988) MK-801, a proposed noncompetitive antagonist of excitatory amino acid neurotransmission, produces phencyclidine-like behavioral effects in pigeons, rats and rhesus monkeys. *J Pharmacol Exp Ther* **245:**969–974.
Lemaire GA and Meisch RA (1985) Oral drug self-administration in rhesus monkeys: interactions between drug amount and fixed ratio size. *J Exp Anal Behav* **44:**377–389.
Lukas SE, Griffiths RR, Brady JV, and Wurster RM (1984) Phencyclidine-analogue self-injection by the baboon. *Psychopharmacology* **83:**316–320.
Marquis KL, Webb MG, and Moreton JE (1989) Effects of fixed ratio size and dose on phencyclidine self-administration. *Psychopharmacology* **97:**179–182.
Marsch LA, Bickel WK, Badger GJ, Rathmell JP, Swedberg MDB, Jonzon B, and Norsten-Hoog C (2001) Effects of infusion rate of intravenously administered morphine on physiological, psychomotor, and self-reported measures in humans. *J Pharmacol Exp Ther* **299:**1056–1065.
Mendelson LG, Kerchner GA, Kalra V, Zimmerman DM, and Leander JD (1984) Phencyclidine receptors in rat brain cortex. *Biochem Pharmacol* **33:**3529–3535.
Moreton JE, Meisch RA, Stark L, and Thompson T (1979) Ketamine self-administration by the rhesus monkey. *J Pharmacol Exp Ther* **203:**303–309.
Panlilio LV, Goldberg SR, Gilman JP, Jufer R, Cone EJ, and Schindler CW (1998) Effects of delivery rate and non-contingent infusions of cocaine on cocaine self-administration in rhesus monkeys. *Psychopharmacology* **137:**253–258.
Parsons CG, Quack G, Bresink I, Baran L, Przegalinski E, Kostowski W, Krzascik P, Hartmann S, and Danysz W (1995) Comparison of the potency, kinetics and voltage-dependency of a series of uncompetitive NMDA receptor antagonists in vitro with anticonvulsive and motor impairment activity in vivo. *Neuropharmacology* **34:**1239–1258.
Renner KE (1964) Delay of reinforcement: a historical review. *Psychol Bull* **61:**341–361.
Slifer BL and Balster RL (1983) Reinforcing properties of stereoisomers of the putative sigma agonists *N*-allylnormetazocine and cyclazocine in rhesus monkeys. *J Pharmacol Exp Ther* **225:**522–538.
Winger G (1993) Fixed ratio and time out changes on behavior maintained by cocaine or methohexital in rhesus monkeys. 1. Comparison of reinforcing strength. *Exp Clin Psychopharmacol* **1:**142–153.
Winger G, France CP, and Woods JH (1991) Intravenous self-injection in rhesus monkeys: comparison of CGS 19755 and phencyclidine-like compounds, in *Excitatory Amino Acids* (Meldrum BS, Moroni E, Simon RP, and Woods JH eds) pp 539–545, Raven Press, New York.
Winger G, Palmer RK, and Woods JH (1989) Drug-reinforced responding: rapid determination of dose-response functions. *Drug Alcohol Depend* **24:**135–142.
Young AM and Woods JH (1981) Maintenance of behavior by ketamine and related compounds in rhesus monkeys with different self-administration histories. *J Pharmacol Exp Ther* **218:**720–727.

Address correspondence to: Dr. Gail Winger, Department of Pharmacology, University of Michigan Medical School, 1301 MSRB III, Ann Arbor, MI 48109-0632. E-mail: gwinger@umich.edu