Psychopharmacology (1996) 128:265–273

ORIGINAL INVESTIGATION

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Progressive ratio and behavioral economic evaluation of the reinforcing efficacy of orally delivered phencyclidine and ethanol in monkeys: effects of feeding conditions

Received: 8 February 1996 / Final version: 22 June 1996

Abstract The effect of feeding conditions on the reinforcing efficacy of orally-delivered drugs was evaluated using a progressive-ratio (PR) paradigm and a behavioral economic analysis of demand. Seven monkeys self-administered phencyclidine (PCP) (0.06, 0.12, 0.25, 0.5, and 1.0 mg/ml) or ethanol (2, 4, 8, 16, and 32% wt/vol) and concurrent water from two drinking spouts under concurrent PR schedules. The ratios increased from 8 to 4096, and 40 liquid deliveries were available after completion of each ratio schedule. The entire range of drug concentrations was presented in nonsystematic order under two feeding conditions, food restriction and food satiation. Drug maintained responses, deliveries and break points were significantly greater than those maintained by water. Food restriction significantly increased the rate of PCP-maintained responses, deliveries and PR break points over the food satiation baseline. There was also a significant interaction between feeding condition and drug concentration. Although ethanol-maintained responses, liquid deliveries and break points consistently increased in five of seven monkeys during food restriction, only drug concentration produced significant differences in these measures. Using break point as a measure of reinforcing efficacy, food restriction increased the reinforcing efficacy of PCP and had a more pronounced effect at higher drug unit prices.

Key words Behavioral economics · Break point · Drug self-administration · Ethanol · Food restriction · Food satiation · PCP · Phencyclidine · Progressive ratio · Rhesus monkeys

Introduction

Increases in drug self-administration during periods of restricted feeding have been well documented (e.g., Carroll 1996); however, the exact nature of this relationship is unclear. The increased drug intake could be a matter of substitution of one type of reinforcement (food) by another (drug), or the absence of food could increase reinforcing efficacy of the self-administered drug. Reinforcing efficacy has been quantified using a number of different schedules such as fixed-ratio (FR) and progressive-ratio (PR) schedules (Griffiths et al. 1979; Winger and Woods 1985; Risner and Cone 1986; Depoortere et al. 1993). Concurrent and discrete-trial choice procedures also have been used to evaluate reinforcing efficacy (Johanson and Schuster 1975; Aigner and Balster 1978; Johanson and Aigner 1981; Woolverton and Johanson 1984). More recently, attempts to quantify reinforcing efficacy of drugs have used behavioral economic measures – the application of microeconomic principles to the consumption of drugs (Bickel et al. 1991; Hursh 1991; Bickel and DeGrandpre 1995).

The behavioral economic measures used to assess reinforcing efficacy are elasticity of demand [consumption plotted as a function of unit price (responses/mg)], intensity of demand (parallel shifts of the demand curve up or down) and P_{max} (an estimate of the unit price or response requirement at which maximal responding occurs) (Hursh 1991; Hursh and Winger 1995). The elasticity of demand is determined from the slope of the demand curve. Slopes less than –1 indicate an elastic demand (i.e., relatively greater decreases in consumption as unit price increases). Slopes greater than –1 indicate an inelastic demand (i.e., relatively small decreases in consumption as unit price increases). Demand for a more efficacious reinforcer would be more resistant to price increases or more inelastic. Intensity of demand refers to the relative consumption at a particular unit price. When a demand curve has been shifted downward in a parallel fashion the interpretation is that there is less intensity of demand for the reinforcer (Hursh 1991). An increase in reinforcing efficacy due to food restriction would result in an increase in intensity of demand. Elasticity and intensity of demand both affect the behavioral economic measure, P_{max}, which represents the price of drug at which maximum responding occurs. It is hypothesized that increased

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reinforcing efficacy (e.g., due to food restriction) would be accompanied by an increase in the P_{max} value. In a recent study of the demand for PCP and ethanol under varied feeding conditions, P_{max} was increased during food restriction (Rodefer et al. 1996). Comer and coworkers (1995) also found that food restriction increased cocaine-base smoking and the intensity of demand for smoking in monkeys.

The conceptual basis of P_{max} is similar to that of break point in PR schedules. In PR schedules, subjects are required to make systematically increasing numbers of responses for successive reinforcers, until the schedule requirement becomes so large that the subjects cease responding. The last completed FR schedule is termed the break point. Break points are considered to be a measure of motivation to work for reinforcers, or a measure of a drug's reinforcing efficacy. Thus, both BP and P_{max} are measures that quantify maximal response output for a fixed delivery of drug.

One of the first uses of PR schedules was by Hodos (1961) to determine the relative reward strength of sweetened milk. Since then, PR tasks have been used in studies that examined intracranial self-stimulation (Hodos 1965), food intake (Spear and Katz 1991) and drug self-administration (Yanagita 1973; Griffiths et al. 1979). A consistent finding in these studies is that increasing magnitudes of the reinforcers or doses of drugs led to increased break points. In experiments that have compared different drugs to obtain relative reinforcing efficacies (Griffiths et al. 1978; Woolverton 1995), rank orders of break points have been established, and results agree with observational and clinical data regarding the relative reinforcing efficacy of different drugs. Consistant with Rodefer et al.'s (1996) findings using P_{max}, Rudski and coworkers (1994) demonstrated that unlimited access to food decreased break points in rats that responded for food under a progressive ratio schedule.

In the present study the effects of feeding conditions on the reinforcing efficacy of PCP and ethanol were assessed using the PR paradigm. This experiment extended the use of PR schedules to the oral route of administration in order to investigate the effects of food restriction on drug intake in monkeys. Additionally, this study sought to demonstrate the feasibility of using concurrent PR schedules to compare the strength of behavior maintained by drug and vehicle (water).

Materials and methods

Subjects

Seven adult male rhesus monkeys (M-A1, M-G1, M-I, M-M1, M-P, M-X, M-Z) served as subjects. The monkeys had extensive previous experience with self-administration of orally-delivered PCP and ethanol under FR schedules, and they had prior exposure to food restriction and satiation conditions. Monkeys were weighed every 2 weeks to monitor body weight. Subjects' weights ranged from 7.5 to 12.5 kg during periods of food restriction and from 9.0 to 14.6 kg during periods of food satiation. Subjects were individually housed in temperature controlled (24°C) colony rooms that were on a 12-h light/dark cycle with lights on at 0700 hours. Each subject had visual, olfactory, and auditory contact with the other monkeys in the colony room. Use of the animals for this experimental protocol was approved by the University of Minnesota Institutional Animal Care and Use Committee (protocol number 9310041). Laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC), and principles of laboratory animal care (NIH publication No. 85–23, revised 1985) were followed.

Apparatus

Subjects were individually housed in stainless steel primate cages (Lab Products, Maywood, N.J.) (83 cm W×76 cm H×100 cm D) that had three solid walls and a solid ceiling. The cage had a barred door as a front wall and a grid floor. Each cage was equipped with a primate swinging perch, and the cages occasionally contained enrichment devices such as Kong toys and polycarbonate mirrors (Primate Products, Redwood City, Calif.) that could be manipulated by the monkeys. Monkey cages were steam cleaned during the post-session time-out every 2 weeks. One side wall of the cage was modified with openings to accomodate an operant work panel that was attached to the cage from the outside. The panel contained two brass drinking spouts in Plexiglas housings, and a 2.5 cm green LED stimulus light was located above each drinking spout. The stimulus light flashed at 10 Hz to signal drug availability and remained solid-on to signal water availability. Drug and water sides were alternated daily. Each brass drinking spout was circumscribed by four small cue lights that were visible through the Plexiglas housing. Two of the cue lights were green and served to indicate drug delivery, and the other two were white to indicate water delivery. The drinking spout and cage made up an electronic drinking circuit that was activated when the monkey made lip contact with the drinking spout. Each successful lip contact resulted in a brief flash of the corresponding green (drug) or white (water) cue lights. Completion of the schedule requirements activated a solenoid drinking valve that dispensed 0.6 ml liquid from 2000 ml plastic reservoirs that were suspended above the work panel. If the monkey removed its mouth from the spout the liquid delivery was terminated. The PR schedule was programmed using MED-PC (Med Associates, Layfayette, Ind.) and was run on an IBM-compatible computer.

Drugs

Phencyclidine hydrochloride was obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, N.C.). The drug was mixed weekly with tap water into a 1.0 mg/ml stock solution that was stored at room temperature. Phencyclidine concentrations of 0.06, 0.12, 0.25, and 0.5 mg/ml were diluted from the stock solution with tap water daily. Concentrations are expressed in terms of the salt. Ethanol (95%) was obtained from University of Minnesota Chemical Storehouse and diluted to achieve 2, 4, 8, 16, and 32% (wt/vol) concentrations. All drug solutions were mixed 19 h prior to session to ensure that they would be delivered at room temperature.

Procedure

Monkeys were initially trained to self-administer orally-delivered PCP under concurrent FR 16 schedules according to methods that have been previously described (Carroll 1982). Ethanol self-administration was accomplished in the PCP-trained monkeys by initially presenting a low concentration (2% wt/vol) along with concurrent water under an FR 4 schedule. The concentration was gradually increased from 2 to 4 to 8%, and then FR was increased from 4 to 8 and then 16. The daily procedure began with a time-out period from 0800 to 1000 hours when computers were prepared for session and reservoirs were filled with liquids. The daily

sessions were conducted from 1000 to 1300 hours and were followed by a 90-min time-out. During this time-out, drug consumption was measured, subjects were fed, solutions were prepared for the next day, and cage pans were washed. The daily food allotment was given to the monkeys at 1400 hours. This consisted of one-quarter of an apple and either a fixed amount of food that maintained monkeys at approximately 85% of their free feeding weight (food restriction) or an unlimited amount (food satiation) of Harlan Teklad monkey diet (8663). The food restriction condition generally required daily amounts of food ranging from 75 to 100 g, while the food satiation daily diet was approximately 300–400 g of monkey chow. The food satiation amount was adjusted so that monkeys always had access to food, but there was not an abundance of food that could be expelled from the cage. There was a 3- to 4-week transition period after each subject's diet condition was changed to allow body weights and drug consumption to stabilize. During this transition period liquid intake data were monitored but not used in the analysis. During the 15.5-h intersession period from 1430 to 0800 hours the next day, monkeys had access to water from both spouts under an FR 1 schedule. During morning and afternoon time-out periods all chamber lights were extinguished, and responding had no programmed consequences.

During the 3-h session drug and water were concurrently available under independently-programmed PR schedules. The steps in the PR program were initially 0.30 log steps beginning from FR 8. However, pilot studies revealed that these increments led to rapid extinction of the subjects' behavior at the higher FRs (cf. Hodos and Kalman 1963). Thus, above FR 128 the PR advanced in 0.15 log steps. The FRs used in the PR program were 8, 16, 32, 64, 128, 178, 256, 356, 512, 712, 1024, 1424, 2048, 2848 and 4096. At session onset, both stimulus lights were illuminated indicating drug and water availability. If an FR schedule was not completed within 30 min, that spout was turned off for the remainder of session, and any subsequent responding on that spout had no programmed consequences. Break point for each PR schedule was defined as the last ratio completed during session. Each day the PR schedule was reset, beginning at FR 8. When the schedule requirements for a spout were completed, the monkey entered a reinforcement phase. Reinforcement was signaled by continuous illumination of the corresponding spout cue lights. The subject had 10 min to complete the reinforcement phase which consisted of 40 liquid deliveries (0.60 ml each; 24 ml total) under an FR 1 schedule. Once the reinforcement phase was completed, there was a 30-s time-out period when stimulus lights were extinguished and responses were not counted before progressing to the next FR schedule. The session was terminated at 1300 hours unless the subject had previously terminated availability of both drinking spouts by exceeding the 30 min allowed for ratio completion.

Each monkey progressed through concurrent PR schedules with either PCP or ethanol and concurrently available water. For each drug the range of concentrations was presented in a nonsystematic order, and each concentration was held constant until at least 3 days of stable behavior were obtained. Since behavior rapidly stabilized after concentration changes, typically only 3–5 days were needed at each concentration to obtain 3 days of stable data. Retests were conducted at selected concentrations, and behavior characteristically returned to previous levels. Stability was defined as no steadily increasing or decreasing trend in responses, break points or deliveries. Each monkey completed both PCP and ethanol protocols in both food satiation and food restriction conditions. One half of the monkeys experienced the food satiation condition first, and one-half received food restriction first. Order of access to PCP and ethanol was also counterbalanced across monkeys. The total time required for one subject to complete these parametric manipulations ranged from 3 to 7 months.

A test of the effectiveness of discriminative stimuli (S^D) used for drug (flashing light) and water (solid light) was conducted following completion of all drug and food manipulations. Subjects were maintained on PCP (0.25 mg/ml) and concurrent water for at least 4 days to establish a stable baseline. Water was then substituted for PCP for 10 days; however, instead of using water stimulus lights on both sides, the flashing stimulus light associated with PCP was used on one side, alternating daily. Water responses, deliveries and break point were compared with the water and PCP stimulus conditions.

Data analysis

The PCP and ethanol data represent the means for the seven monkeys over three daily sessions. Standard error of the means (SEMs) were calculated from the means for each subject. Repeated measures analyses of variance (ANOVAs) were performed separately for PCP and ethanol responses, deliveries, and break point. Criterion levels of statistical significance were set a priori at $P<0.05$. Statistical analyses were generated using StatView and SuperANOVA (Abacus Concepts, Berkeley, Calif.) on a Power Macintosh computer.

Results

Responding maintained by PCP was higher than that maintained by ethanol, and there was higher intersubject variability under the PCP condition (Fig. 1). The main effect of feeding condition on PCP-maintained responding [$F(1, 6)=11.04$, $P<0.05$], and the interaction between feeding condition and PCP concentration were statistically significant [$F(4, 24)=3.60$, $P<0.05$], but there were no significant differences in responding maintained by PCP due to PCP concentration [$F(4, 24)=1.86$, $P>0.05$].

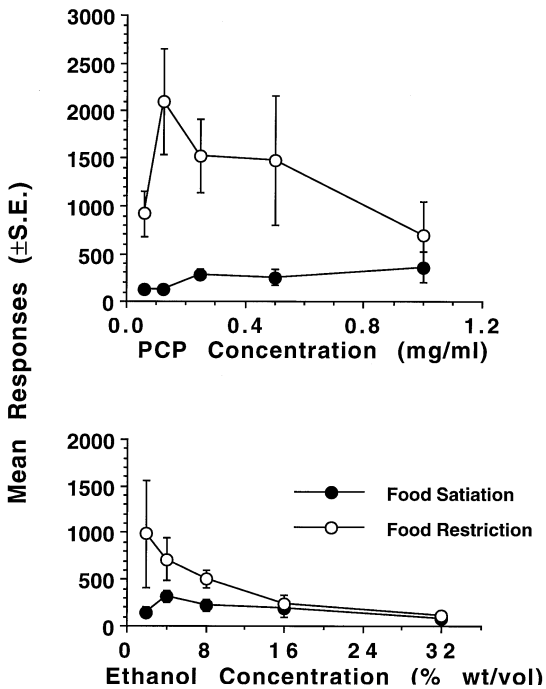

Fig. 1 Mean number of lip contact responses for PCP (*top frame*) or ethanol (*bottom frame*) per session. Responses are plotted as a function of drug concentration. *Open circles* represent the food restriction condition, while *filled circles* represent the food satiation condition. Each point represents a mean for seven monkeys over the last 3 days of stable behavior. *Vertical bars* indicate 2 SEMs

Main effects of feeding condition, ethanol concentration and the interaction between feeding condition and ethanol concentration were not statistically significant with regard to ethanol responding ($P>0.05$). Both drugs maintained response rates in excess of the concurrently available water vehicle, revealing the reinforcing effects of drugs under concurrent PR schedules (water data are not shown).

There was no significant main effect for PCP concentration on break point (Fig. 2). However, statistically significant differences were obtained for the main effect of feeding condition [$F(1, 6)=10.43$, $P<0.05$] and the interaction between feeding condition and PCP concentration [$F(4, 24)=3.1$, $P<0.05$]. The BP due to feeding condition was elevated across all PCP concentrations, with a peak increase at the 0.12 mg/ml concentration. During ethanol self-administration, only the main effect of ethanol concentration was statistically significant [$F(4, 24)=3.34$, $P<0.05$]. Neither the main effect of feeding condition nor the interaction between feeding condition and ethanol concentration was statistically significant. However, for five out of seven monkeys (all except M-A and M-G) the break point maintained by ethanol consistently increased for all concentrations during food restriction compared to food satiation.

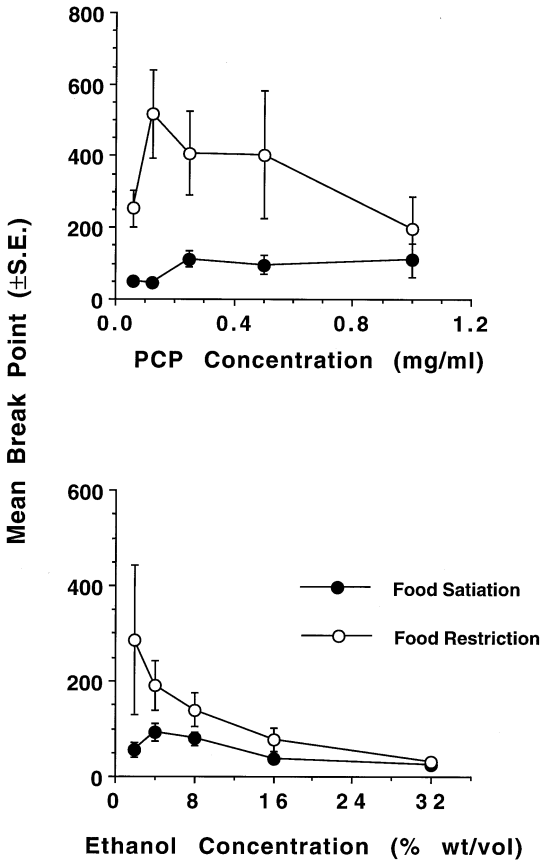

Fig. 2 Mean break point (BP) for PCP (*top frame*) or ethanol (*bottom frame*) maintained responding is plotted as a function of drug concentration. *Open circles* represent the food restriction condition, while *filled circles* represent the food satiation condition. Each point represents a mean for seven monkeys over the last 3 days of stable behavior. *Vertical bars* indicate 2 SEMs

Break point data for water responding are presented in Table 1. PCP maintained break points that were in excess of those maintained by water at all concentrations and under both feeding conditions (Table 1). However, ethanol break points were not consistently higher than water break points under food satiation conditions. As ethanol concentration increased, water intake increased under the food restriction condition but not under the food satiation condition. There was a significant main effect of ethanol concentration on water deliveries [$F(4, 24)=3.22$, $P<0.05$].

Deliveries of PCP while under the food restriction condition were greater than those under the food satiation condition across all concentrations of PCP (Fig. 3, upper frame). The main effect of feeding condition [$F(1, 6)=26.18$, $P<0.05$] and the interaction of feeding condition and PCP concentration were statistically significant [$F(4, 24)=6.21$, $P<0.05$]. However, the main effect of PCP concentration was not statistically significant [$F(4, 24)=1.71$, $P>0.05$]. Water deliveries were consistently lower than PCP deliveries at all concentrations and under both feeding conditions.

With regard to ethanol self-administration, only the main effect of drug concentration on deliveries was statistically significant [$F(4, 24)=16.70$, $P<0.05$] (Fig. 3, lower frame). Neither the main effect of feeding condition nor the interaction of feeding condition with ethanol concentration was statistically significant ($P>0.05$). Examination of individual data revealed that five out of seven monkeys (again, all except M-A and M-G) increased their ethanol deliveries at each concentration when food restricted compared to when they were food satiated, resulting in the parallel elevation of the mean delivery concentration curve. Water deliveries were lower than ethanol deliveries under both feeding conditions, except at the highest ethanol concentration where water deliveries slightly exceeded ethanol deliveries.

After completion of each ratio in the PR series, 40 liquid deliveries were available under an FR 1 schedule. The percentage of deliveries consumed out of the total 40 PCP deliveries available ranged from 86.3 to 100% across the range of concentrations, although these values did not vary systematically across concentration or feeding condition (Table 2). The percentage of total available ethanol deliveries earned was lower, ranging from 43.3 to 100%. The lowest percentage (43.3%) of available ethanol deliveries earned was at the highest concentration (32% wt/vol), possibly due to aversive taste. There was no difference in percentage of PCP or ethanol deliveries earned as a function of feeding condition. In contrast to drug intake, the percentage of available water deliveries obtained was lower, ranging from 47 to 65.6% when PCP was concurrently available and from 37.6 to 88.9% when ethanol was concurrently available. These data suggest that the monkeys may

Table 1 Mean break point (BP) (±SEM) for PCP and ethanol with concurrent water as a function of drug dose during food satiation and restriction

	PCP conc. (mg/ml)	Break point				
		0.06	0.12	0.25	0.5	1.0
Food satiation	PCP	47.71* (10.9)	44.09 (6.6)	111.99 (21.6)	95.49 (27.2)	109.44 (46.4)
	Concurrent water	18.96 (9.1)	27.51 (16.3)	35.53 (19.9)	27.77 (11.9)	42.76 (19.7)
Food restriction	PCP	252.37 (49.6)	517.34 (122.1)	407.80 (116.4)	403.77 (117.0)	198.27 (90.1)
	Concurrent water	32.76 (20.3)	38.10 (18.5)	64.11 (35.1)	82.34 (43.8)	67.24 (46.4)
	Ethanol conc. (% wt/vol)	Break point				
		2%	4%	8%	16%	32%
Food satiation	Ethanol	55.90 (15.1)	92.56 (17.9)	78.49 (13.4)	36.96 (7.9)	23.24 (5.2)
	Concurrent water	47.34 (14.3)	24.00 (8.8)	49.54 (25.9)	43.00 (19.6)	41.53 (15.0)
Food restriction	Ethanol	286.19 (157.1)	190.29 (52.1)	139.90 (36.4)	76.96 (24.7)	30.47 (7.1)
	Concurrent water	32.00 (15.9)	40.60 (20.2)	28.56 (12.4)	30.67 (18.3)	42.39 (22.1)

* Each number represents a mean (±SEM) of seven monkeys over the last 3 days of stable behavior

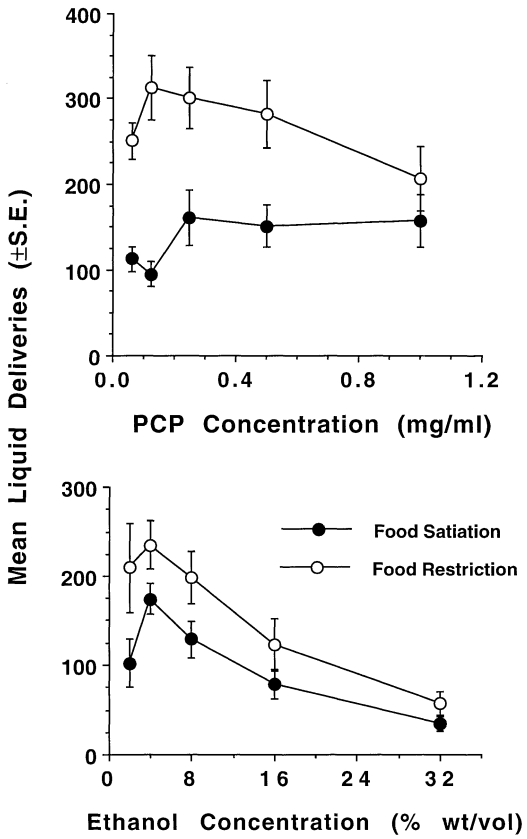

Fig. 3 Mean number of liquid deliveries of PCP (*top frame*) or ethanol (*bottom frame*) per session is plotted is a function of drug concentration. *Open circles* represent the food restriction condition, while *filled circles* represent the food satiation condition. Each point represents a mean for seven monkeys over the last 3 days of stable behavior. *Vertical bars* indicate 2 SEMs

have become satiated for water but not the drug solutions.

For both PCP and ethanol the demand curve was shifted left and downward under food satiation conditions relative to food restriction, indicating a decrease in the intensity of demand for the drugs (Fig. 4). The dashed lines on the demand curves refer to data previously collected on the same monkeys using fixed drug concentrations (0.25 mg/ml PCP; 8% wt/vol ethanol) and FR changes (4, 8, 16, 32, 64 and 128) to obtain demand curves during food satiation and restriction (Rodefer et al. 1996). Only a few unit prices from the studies were similar, and a comparison of these data illustrates that drug consumption was shifted downward at those prices under the PR schedule relative to the FR schedule.

The mean responses, break points and liquid deliveries are shown for the last day PCP and water were concurrently available (Table 3, top section). For the first and tenth days, water was available with a water S^D on one side and a PCP S^D on the other side (Table 3, middle section), and the first day PCP was reinstated with concurrent water (Table 3, lower section). Replacement of PCP with water resulted in a marked decrease in all measures which stabilized within 2 or 3 days. When PCP was reinstated, there was an immediate return to high levels of responding. Two-tailed *t*-tests conducted on each of the 10 days of water substitution revealed no significant differences in any of the measures between water with PCP S^D and water with water S^D ($P>0.05$). Comparisons of PCP- and water-maintained behavior on the days preceding (baseline) and following PCP reintroduction were also made with one-tailed *t*-tests, and differences were significant ($P<0.05$).

Table 2 Mean percentage of total available liquid deliveries (±SEM) consumed per session during food satiation and restriction

	PCP conc. (mg/ml)	Percentage of deliveries consumed				
		0.06	0.12	0.25	0.5	1.0
Food satiation	PCP	93.9 (7.4)	78.5 (12.3)	100 (20.4)	94.2 (15.4)	98.6 (19.0)
	Concurrent water	54.3 (23.0)	65.6 (17.8)	52.8 (23.9)	64.3 (28.6)	57.2 (24.1)
Food restriction	PCP	100 (8.8)	97.8 (11.9)	100 (12.8)	100 (14.1)	86.3 (15.9)
	Concurrent water	50.3 (26.0)	54.8 (23.8)	64.6 (22.7)	60.5 (26.9)	47 (26.6)
	Ethanol conc. (% wt/vol)	Percentage of deliveries consumed				
		2%	4%	8%	16%	32%
Food satiation	Ethanol	84.9 (19.4)	100 (10.9)	80.7 (12.9)	65.2 (14.9)	43.3 (11.3)
	Concurrent water	58.3 (18.6)	70.7 (26.4)	37.6 (11.3)	65.4 (23.7)	72.1 (24.4)
Food restriction	Ethanol	74.7 (18.0)	97.9 (11.2)	99 (14.1)	77.1 (18.8)	71.1 (17.9)
	Concurrent water	46.7 (18.1)	59.4 (25.1)	81.6 (19.1)	88.9 (15.6)	73.3 (19.0)

Discussion

Responses, deliveries and break points for both PCP and ethanol exceeded those measures for the water vehicle (except at the higher ethanol concentrations), indicating that both drugs were functioning as reinforcers under the PR paradigm. The lack of differences at the high ethanol concentrations (16% and 32% wt/vol) may have been due to aversive taste. The monkeys spent a majority of their time with the drinking spout and PR schedule associated with drug. Water-maintained responding was low and tended to occur early in the session. Drug deliveries that occurred in the reinforcement phase under the FR 1 schedule generally followed an inverted U-shaped function of concentration, although responding and break point under the PR schedule did not vary significantly with concentration. Thus, the PR schedule did not produce a characteristic inverted U-shaped dose effect curve with all dependent measures. While inverted U-shaped dose-effect functions have been demonstrated with i.v. drug self-administration and PR schedules (Griffiths et al. 1979), the lack of a distinct dose-effect function has been reported recently (French et al. 1995). The differences among these findings may reflect differential acquisition procedures, subject history, route of administra-

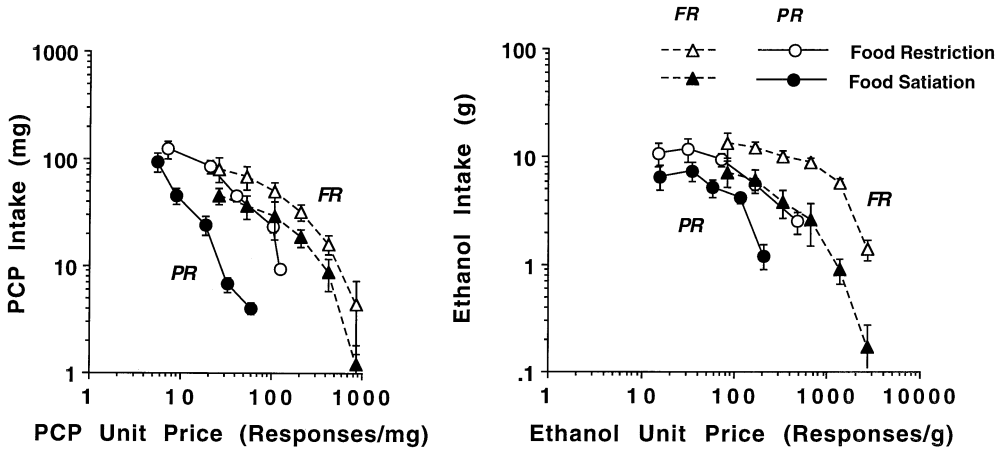

Fig. 4 Mean PCP intake (mg) per session is presented in the *left frame* as a function of PCP unit price (responses/mg), and mean ethanol intake (g) per session is plotted in the *right frame* as a function of ethanol unit price (responses/g). *Open symbols* represent the food restriction condition, while *filled symbols* represent the food satiation condition. Data represented by *circles* and *solid lines* are from the present experiment, while data represented by *triangles* and *dashed lines* are from the same monkeys in a previously published study that manipulated unit price by holding drug concentration constant and changing FR value. Each point is a mean of six or seven monkeys over the last 3 or 5 days (present and previous data, respectively) of stable behavior. *Vertical bars* indicate 2 SEMs

Table 3 Effect of the PCP S^D on extinction behavior

			Means (±SEM)					
			Responses		Break point		Liquid deliveries	
(*n*=6)	Last	PCP	2120.7	(315.9)	543.3	(82.5)	338.5	(29.2)
	Day	H_2O	228.8	(141.8)	60.7	(37.1)	94.5	(53.1)
(*n*=6)	First	H_2O*	236.0	(94.7)	88.3	(22.0)	153.8	(28.3)
	Day	H_2O	149.5	(109.3)	58.7	(39.7)	80.7	(41.4)
	Tenth	H_2O*	156.0	(60.3)	65.3	(21.1)	122.3	(27.6)
	Day	H_2O	44.2	(18.0)	21.3	(9.8)	69.5	(26.3)
(*n*=5)	First	PCP	2456.0	(378.2)	663.2	(112.3)	389.8	(16.25)
	Day	H_2O	173.4	(106.2)	172.0	(96.1)	206.3	(59.3)

* PCP S^D (flashing light) on one side, water S^D (solid light) on the other side, alternating daily

tion, reinforcement magnitude, the stepwise ratio increments, and/or other methodological factors. Further work is needed to determine the conditions that allow the PR schedule to be most sensitive to reinforcing effects of drugs. Responding for ethanol (Fig. 1) as a function of concentration was not characterized by an inverted-U-shaped curve typical for responding maintained by an FR schedule. However, ethanol deliveries and, to a lesser extent, ethanol break point, followed an inverted-U-shaped curve. Peak ethanol consumption was less than peak PCP consumption, and ethanol generated more shallow curves. Traditional inverted U-shaped concentration-response curves have previously been demonstrated for ethanol consumption (Henningfield and Meisch 1978).

The effect of feeding condition was clearly observed in both ethanol and PCP responses, break point and deliveries. The upward shift in the curve due to food restriction was greater at lower drug concentrations for both PCP and ethanol. In behavioral economic terms, lower concentrations represent higher unit prices (responses/mg). This finding concurred with previous studies in which unit price was varied by changing concentration (Carroll et al. 1991) and FR value (Rodefer et al. 1996). Thus, food restriction produces greater increases in drug self-administration as the cost of drug increases.

Differences in PR performance (Fig. 2) between PCP and ethanol may represent a difference in reinforcing efficacy between the two drugs. Alternatively, there have been reports that high doses of certain drugs have aversive properties (Wise et al. 1976). Such an observation is especially relevant in oral self-administration studies where the taste or olfactory effects of a drug such as ethanol can create difficulties in establishing a consistent self-administration pattern. The aversive taste qualities of ethanol have been documented previously (Mello and Mendelson 1971). A second hypothesis that might explain differences between break point for ethanol and PCP is that caloric properties of ethanol impact upon the self-administration of the drug itself. While this possibility cannot be excluded from consideration, the caloric benefits from an 8% (wt/vol) ethanol solution are minimal, especially when the modest increases in ethanol intake are taken into account.

The shifts in maximal responding (break point) for ethanol and PCP (Table 1 and Fig. 2) due to feeding condition are consistent with previous findings that demonstrated food restriction increased the P_{max} values of PCP and ethanol. These data suggest that food restriction increased the reinforcing value of PCP and ethanol (Rodefer et al. 1996). Under food restriction in the PCP condition, the break point of water increased as PCP concentration increased. It seemed that this behavior served to dilute the more concentrated PCP solutions, because higher concentrations of PCP can be aversive, rather than being an artifact of general increased responding due to food restriction.

While manipulation of the feeding condition did not result in a significant effect on the break point of ethanol across the range of ethanol concentrations, results suggest a difference due to feeding condition at the lower ethanol concentrations. When the feeding conditions were compared for subjects responding for ethanol, two issues were readily apparent. First, maximal responding occurred at a lower ethanol concentration (2% wt/vol) under food restriction compared to food satiation (4% wt/vol) conditions. Second, this leftward shift resulted in a four-fold increase in ethanol break point at the lowest concentration. A similar shift in maximal break point from the 0.25 mg/ml concentration of PCP to 0.12 mg/ml was observed for PCP during food restriction. The magnitude of the break point increase due to increased responding for PCP in the food restriction condition was greater at the lower drug concentrations.

In a previous study that examined the reinforcing efficacy of PCP and ethanol under food restriction and food satiation conditions using FR schedules, Rodefer and coworkers (1996) reported that food restriction increased P_{max} (an estimate of the response requirement at which maximal responding occurred) for both PCP and ethanol. The rightward shift in P_{max} due to food restriction was greater for ethanol than for PCP; a more appropriate comparison could be made with normalized demand curves (Hursh and Winger 1995), but such an analysis was beyond the scope of this project. In the current study, larger increases in break point due to food restriction were seen with PCP rather than ethanol. Thus, while both break point and P_{max} appear to be measures of reinforcing efficacy based on maximum response output, there are differences in sensitivity to the effects of feeding conditions between FR and PR schedules.

One explanation for these differences in sensitivity may be that the FR and PR schedules assess different components of behaviors associated with the reinforcement process. Winger and Woods (1985) examined various doses of IV cocaine and nomifensine under both FR and PR schedules to evaluate relative effectiveness of drug maintained behavior. Their findings suggested that PR and FR schedules produced similar relative reinforcing data for cocaine and nomifensine. However, McGregor and Roberts (1993, 1995) found evidence for differences between FR and PR schedules. They administered injections of the D_1 antagonist SCH 23390 into different brain regions and examined self-administration of cocaine under different schedules of reinforcement. Different patterns of behavior were observed, depending upon the injection site and the schedule of reinforcement, and they suggested that FR and PR schedules measure different and distinct aspects of cocaine reinforcement. In a similar fashion, rats with septal lesions displayed lowered responding for food under FR schedules in contrast to PR schedules (Poplawsky and Cohen 1991), despite the fact that the lesions did not alter the reward value of food (determined by a behavioral economic analysis).

Another possible explanation for differences in the food restriction effect between PCP and ethanol might involve the non-reinforcing effects of the drugs (e.g., direct stimulus effects). Recently, Woolverton (1995) examined the relative reinforcing efficacy of cocaine and procaine using the PR paradigm. Using a single drug delivery per schedule completed and by varying the intertrial interval to allow for any stimulus effects to dissipate, Woolverton demonstrated cocaine's greater potency with minimal confounding effects. The current study results would also be minimally affected by direct stimulus effects of PCP or ethanol because of the delayed onset of effects for drugs consumed orally. Also, while the subjects had the duration of the 3-h session to self-administer drugs, it was frequently the case that most drug intake occurred in the first hour of session. A comparison of previous findings using FR schedules suggested that the monkeys' drinking topography was not impacted by PR schedules (Carroll 1985; Carroll and Rodefer 1993).

A third possibility for the observed differences between PCP and ethanol under food restriction may involve metabolic pathways for the two drugs. Given that ethanol is degraded via cytochrome P450 enzymes, it is conceivable that decreased food intake may activate these enzymatic systems and lead to lower serum ethanol concentrations. Subsequently, subjects might demonstrate increased responding to compensate for decreased ethanol levels. The metabolism of phencyclidine is accomplished though glucuronide conjugation in the liver. Since glucuronic acid is derived from glucose, restricted food intake may impact upon glucose availability and thus decrease metabolism of PCP. If food restriction did serve to decrease the metabolism of PCP, one might expect to observe smaller increases in responding due to a longer duration of circulating PCP. Since food restriction does lead to large increases in PCP reinforced responding, decreased food intake appears to have a negligible effect on behaviors resulting from any altered metabolism of PCP.

While regarded as a useful tool in ascertaining reinforcing efficacy, the PR paradigm has the limitations of requiring unequal response requirements for increased drug delivery. In such a paradigm, the drug intake is often an all-or-nothing phenomenon and can be most problematic for those studies that only use one reinforcer delivery per schedule completion. Studies that have utilized multiple deliveries per schedule have tended to avoid this problem and have the added ability of being able to discern a more graded response pattern (Griffiths et al. 1979; Woolverton 1995). The use of 40 liquid deliveries after each completed ratio in the present study resulted in intakes over the 3-h sessions that were similar to those obtained with FR schedules (Rodefer et al. 1996). However, when the present PR data were plotted as a demand curve (Fig. 4), consumption was lower than that obtained in the previous study in which FR values were manipulated (Rodefer et al. 1996) for those unit prices that overlapped between studies. In the present study, unit price (responses/mg or responses/g) was a dependent measure. The unit price may have been higher if fewer than 40 liquid deliveries were offered for reinforcement. In fact, if the PR curves were shifted to the right (to a range of higher unit prices), the PR-generated demand curves would overlap the FR-generated demand curves. Further manipulations such as this would be needed to determine whether PR-generated demand curves meet the assumption of functional equivalence of response requirement and drug dose as constituents of unit price (responses/mg) (Bickel et al. 1991).

In summary, results from the present study demonstrated that concurrent PR schedules could be used to differentiate the reinforcing effects of orally-delivered drugs (PCP and ethanol) versus the water vehicle. The PR data indicated increased reinforcing efficacy of orally-delivered PCP and lower doses of ethanol under food restriction compared to food satiation conditions. This result was similar to that previously reported using FR schedules and a behavioral economic analysis of demand; food restriction had a greater effect at higher unit prices for drug.

Acknowledgements The authors are grateful to Vincent Hunt for his technical assistance in developing the computer program for this experiment, to Dr. Adande Mattox and Pamela Keel for their critical review of the manuscript, and to Kimberly DeRoche, Scott Resig and Sherry Thompson for assisting with the experiments. This research was supported by National Institute on Drug Abuse Grants R01 DA02486 (M.E. Carroll) and T32 DA 07097 (S.B. Sparber, P.I.; M.E. Carroll, Investigator).

References

Aigner TG, Balster RL (1978) Choice behavior in rhesus monkey: cocaine versus food. Science 201: 534–535

Bickel WK, DeGrandpre RJ (1995) Price and alternatives: suggestions for drug policy from psychology. Int J Drug Policy 6: 93–105

Bickel WK, DeGrandpre RJ, Hughes JR, Higgins ST (1991) Behavioral economics of drug self administration. I. Functional equivalence of response requirement and drug dose. Life Sci 47: 1501–1510

Carroll ME (1982b) Rapid acquisition of oral phencyclidine self-administration in food-deprived and food-satiated rhesus monkeys. Pharmacol Biochem Behav 17: 341–346

Carroll ME (1996) Interactions of food and addiction. In: Niesink RJM and Kornet MLMW (eds) Behavioral toxicology and addiction: food, drugs and environment. Open University Press, The Netherlands, in press

Carroll ME, Rodefer JS (1993) Income alters choice between drug and an alternative nondrug reinforcer in monkeys. Exp Clinical Psychopharmacol 1: 110–120

Carroll ME, Carmona GN, May SA (1991) Modifying drug-reinforced behavior by altering the economic conditions of the drug and nondrug reinforcer. J Exp Anal Behav 56: 361–376

Comer SD, Turner DM, Carroll ME (1995) Effects of food restriction on cocaine base smoking in rhesus monkeys. Psychopharmacology 119: 127–132

Depoortere RY, Li DH, Lane JD, Emmett-Oglesby MW (1993) Parameters of self-administration of cocaine in rats under a progressive-ratio schedule. Pharmacol Biochem Behav 45: 539–548

French ED, Lopez M, Peper S, Kamenka J-M, Roberts DCS (1995) A comparison of the reinforcing efficacy of PCP, the PCP derivatives TCP and BTCP, and cocaine using a progressive ratio schedule in the rat. Behav Pharmacol 6: 223–228

Griffiths RR, Brady JV, Snell JD (1978) Progressive-ratio performance maintained by drug infusions: comparision of cocaine, diethylpropion, chlorphentermine, and fenfluramine. Psychopharmacology 56: 5–13

Griffiths RR, Bradford LD, Brady JV (1979) Progressive ratio and fixed ratio schedules of cocaine-maintained responding in baboons. Psychopharmacology 65: 125–136

Henningfield JE, Meisch RA (1978) Ethanol drinking by rhesus monkeys as a function of concentration. Psychopharmacology 57: 133–136

Hodos W (1961) Progressive ratio as a measure of reward strength. Science 134: 943–944

Hodos W (1965) Motivational properties of long durations of rewarding brain stimulation. J Comp Physiol Psychol 9: 219–224

Hodos W, Kalman G (1963) Effect of increment size and reinforcer volume on progressive ratio performance. J Exp Anal Behav 6: 387–392

Hursh SR (1991) Behavioral economics of drug self-administration and drug abuse policy. J Exp Anal Behav 56: 377–393

Hursh SR, Winger G (1995) Normalized demand for drugs and other reinforcers. J Exp Anal Behav 64: 373–384

Johanson C-E, Aigner T (1981) Comparison of the reinforcing properties of cocaine and procaine in rhesus monkeys. Pharmacol Biochem Behav 15: 49–53

Johanson C-E, Schuster CR (1975) A choice procedure for drug reinforcers: cocaine and methlyphenidate in the rhesus monkey. J Pharmacol Exp Ther 193: 676–688

Mello NK, Mendelson JH (1971) The effects of drinking to avoid shock on alcohol intake in primates. In: Roach MK, McIsaac WM Creaven PJ (eds) Biological aspects of alcohol. University of Texas Press, Austin, Tex., pp 313–340

McGregor A, Roberts DC (1993) Dopaminergic antagonism within the nucleus accumbens or the amygdala produces differential effects on intravenous cocaine self-administration under fixed and progressive ratio schedules of reinforcement. Brain Res 624: 245–252

McGregor A, Roberts DC (1995) Effect of medial prefrontal cortex injections of SCH 23990 on intravenous cocaine self-administration under both a fixed and progressive ratio schedule of reinforcement. Behav Brain Res 67: 75–80

Poplawsky A, Cohen SL (1991) Septal lesions lower responding under fixed-ratio schedules of reinforcement. Behav Neural Biol 56: 119–128

Risner ME, Silcox DL (1981) Psychostimulant self-administration by beagle dogs in a progressive-ratio paradigm. Psychopharmacology 75: 25–30

Rodefer JS, DeRoche KK, Lynch WA, Carroll ME (1996) Feeding conditions alter the demand for phencyclidine and ethanol: a behavioral economic analysis. Exp Clin Psychopharmacology 4: 61–67

Rudski JM, Billington CJ, Levine AS (1994) Naloxone's effects on operant responding depend upond level of deprivation. Pharmacol Biochem Behav 49: 377–383

Spear DJ, Katz JL (1991) Cocaine and food as reinforcers: effects of reinforcer magnitude and response requirement under second-order fixed-ratio and progressive-ratio schedules. J Exp Anal Behav 56: 261–275

Winger G, Woods JH (1985) Comparision of fixed-ratio and progressive-ratio schedules of maintenance of stimulant drug-reinforced responding. Drug Alcohol Depend 15: 123–130

Wise RA, Yokel RA, de Wit H (1976) Both positive reinforcement and conditioned aversion from amphetamine and apomorphine in rats. Science 191: 1273–1275

Woolverton WL (1995) Comparison of the reinforcing efficacy of cocaine and procaine in rhesus monkeys responding under a progressive-ratio schedule. Psychopharmacology 120: 296–302

Woolverton WL, Johanson C-E (1984) Preference in rhesus monkeys given a choice between cocaine and *d,l*-cathinone. J Exp Anal Behav 41: 35–43

Yanagita T (1973) An experimental framework for evaluation of dependence liability of various types of drugs in monkeys. Proc 5th Int Cong Pharmacol 1: 7–17