JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 2011, **95,** 75–89 NUMBER 1 (JANUARY)

EFFECTS OF DAILY MORPHINE ADMINISTRATION AND DEPRIVATION ON CHOICE AND DEMAND FOR REMIFENTANIL AND COCAINE IN RHESUS MONKEYS

TAMMY WADE-GALUSKA[1,2], CHAD M. GALUSKA[3], AND GAIL WINGER[1]

[1]UNIVERSITY OF MICHIGAN
[2]UNIVERSITY OF SOUTH CAROLINA-SALKEHATCHIE
[3]COLLEGE OF CHARLESTON

Choice procedures have indicated that the relative reinforcing effectiveness of opioid drugs increases during opioid withdrawal. The demand curve, an absolute measure of reinforcer value, has not been applied to this question. The present study assessed whether mild morphine withdrawal would increase demand for or choice of remifentanil or cocaine. Four rhesus monkeys chose between remifentanil and cocaine during daily sessions. Demand curves for both drugs were subsequently obtained. The effects of daily injections of 3.2 mg/kg morphine on both choice and demand for these drugs was assayed 3 and 20.5 hr after each morphine injection, and then during a postmorphine period. Three hours following morphine injections, choice of remifentanil over cocaine decreased and demand for remifentanil—but not cocaine—became more elastic. During morphine withdrawal (20.5 hr postinjection), choice of remifentanil increased and remifentanil demand became more inelastic in 3 of 4 monkeys. Cocaine demand also became more inelastic during this period. Four to five weeks following the morphine regimen, demand for both drugs was more inelastic relative to the initial determination. The results suggest that both the relative and absolute reinforcing effectiveness of remifentanil decreased following morphine administration and increased during morphine withdrawal. The absolute reinforcing effectiveness of cocaine also increased during morphine withdrawal. In addition, extended exposure to drug self-administration and/or exposure to the morphine regimen produced long-term increases in demand for both drugs.

Key words: drug self-administration, behavioral economics, choice, remifentanil, cocaine, lever press, rhesus monkeys

Studies of whether the reinforcing effects of opioids are increased as the result of opioid withdrawal are important for several reasons. First, in dependent individuals, opioids may serve not only as positive reinforcers, but their self-administration also may be maintained by negative reinforcement. Opioid withdrawal has been characterized as an aversive condition (Downs & Woods, 1975), which is quickly ameliorated by opioid self-administration (Gerak, Galici, & France, 2009). Second, there is the possibility that withdrawal-induced increases in the reinforcing effects of opioids, particularly if they are long-term, may contribute to relapse to opioid abuse in recovering opioid abusers. Two procedures frequently have been employed to reflect withdrawal-induced increases in the reinforcing effectiveness of opioids: the measurement of changes in rates of responding and number of injections self-administered, and the measurement of changes in choice of an opioid over a nonopioid option.

Gerak et al. (2009) evaluated the effects of chronic, noncontingent morphine administration on the self-administration of a range of heroin and cocaine doses in rhesus monkeys. Their regimen of twice-daily morphine administration, which involved increasing the dose of morphine over a period of several weeks, resulted in dependence as measured by signs of withdrawal. Heroin and cocaine self-administration then was assessed following varying durations of morphine deprivation. Five hours after an injection of morphine, rates of responding maintained by both heroin and cocaine were decreased relative to baseline.

The University of Michigan is accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). As such, procedures used in this experiment were conducted in accordance with the National Research Council's (1996) Guide for the Care and Use of Laboratory Animals and approved by the University Committee on Care and Use of Animals.

Support from the National Institute on Drug Abuse, DA 015449 and DA 023992 is gratefully acknowledged. The authors also thank Amy Hall and Graham Flory for their technical assistance with this research, and Dr. James H. Woods for his comments on the manuscript.

Correspondence may be addressed to Tammy Wade-Galuska, University of South Carolina-Salkehatchie, 807 Hampton St. Walterboro, SC 29488 (e-mail: twadegal@mailbox.sc.edu).

doi: 10.1901/jeab.2011.95-75

However, 17 hr of morphine deprivation led to increases in the number of injections of small cocaine doses (less than 10 μg/kg/infusion) and 29 hr of morphine deprivation led to increases in the number of injections of all heroin doses tested (ranging from 5.6 to 560 μg/kg/infusion). Following the completion of chronic morphine administration, the number of injections of small heroin doses, particularly 5.6 μg/kg/infusion and smaller, remained markedly elevated relative to injections earned before and during morphine administration. The authors attributed this effect to conditioned reinforcement; specifically, they postulated that the cues paired with heroin and cocaine infusions became more effective in maintaining responding during opioid withdrawal than they had been prior to morphine exposure. These cues then maintained their reinforcing effectiveness for many weeks following withdrawal.

Studies in rats support this conclusion; for example, rats trained to self-administer heroin show marked increases in responding for cues that were previously paired with heroin. This occurred for rats that had been heroin abstinent for 4 weeks as well as for those that had been heroin abstinent for 1 week (Zhou et al. 2004).

An alternative evaluation of opioid-maintained responding during opioid withdrawal involves measuring changes in choice of an opioid versus a non-opioid reinforcer during opioid withdrawal. Negus (2006) assessed choice between a range of heroin doses and food in nondependent and heroin-dependent rhesus monkeys. At small or zero doses of heroin, the monkeys showed a near-exclusive preference for food; as the dose of heroin was increased, preference shifted from food to heroin. When the monkeys were given sufficient access to heroin to produce opioid dependence and were then heroin-restricted, opioid withdrawal was observed and the choice of heroin over food was increased substantially at all but the largest dose.

Earlier findings regarding choice between heroin and food are consistent with those of Negus (2006). Griffiths, Wurster, and Brady (1981) found that infusions of morphine produced dose-dependent decreases in selection of heroin over food in baboons whereas infusions of the opioid antagonist naloxone produced dose-dependent increases in selection of heroin. The authors suggested that morphine and naloxone had altered choice behavior by interacting with the reinforcing properties of heroin. Given the large dose of heroin the baboons obtained (1.0 mg/kg/injection), it is likely that naloxone produced increases in choice of heroin in part because it elicited opioid withdrawal.

Another way to evaluate changes in the effectiveness of a reinforcer is demand-curve analysis (e.g., Bickel, DeGrandpre, Higgins, & Hughes 1990; Hursh & Silberberg, 2008; Hursh & Winger, 1995). Here, the consumption of a commodity, or reinforcer, is measured as its price (response requirement) is altered. Initially as the price (defined here as the response requirement / dose) of a reinforcer is increased, consumption is defended by increases in responding and remains relatively unchanged. With further increases in price, consumption decreases. When plotted on log–log coordinates, the rate at which consumption decreases as a function of price is termed elasticity of demand. Generally speaking, a reinforcer that is more effective at maintaining behavior engenders a less elastic demand curve, with consumption decreasing at a slower rate as a function of price, when compared with a reinforcer that is less effective at maintaining behavior.

In the present experiment, both a choice procedure and a demand procedure were used to assess the effects of mild morphine withdrawal on the reinforcing effectiveness of the ultrashort-acting μ-opioid agonist remifentanil and the psychostimulant cocaine in rhesus monkeys. After (premorphine) measures of choice and demand for cocaine and remifentanil were obtained, 4 monkeys were given daily injections of 3.2 mg/kg morphine. This method of morphine administration has been used previously to produce mild opioid dependence in rhesus monkeys (France & Woods, 1989; Winger & Woods, 2001). Choice between cocaine and remifentanil was assessed for at least 2 weeks in sessions conducted 3 and 20.5 hr after each morphine injection. When choice of cocaine and remifentanil was stable, demand for each self-administered drug was reassessed while daily morphine injections continued. The morphine injections were then stopped; 4 to 5 weeks following the final morphine injection, demand for cocaine and remifentanil was assessed for a third time. It

was predicted that, while overall responding would be suppressed 3 hr following morphine administration, responding for remifentanil would be affected to a greater extent than responding for cocaine at this time. At 20.5 hr following morphine, choice and demand for remifentanil was expected to increase relative to choice and demand for cocaine. It also was expected that the latter changes would be maintained, at least to some extent, beyond the period of daily morphine administration.

METHOD

Subjects

Subjects were 4 adult rhesus monkeys (*Macaca mulatta*), 3 male and 1 female. All monkeys had a history of self-administering drugs, including cocaine and remifentanil, according to fixed-ratio (FR) schedules. Experimental sessions were conducted in the home cages. The monkeys were fed high-protein monkey biscuits twice daily and fruit once daily to maintain their adult body weights. Water was continuously available and environmental enrichment was provided on a rotating basis.

Apparatus

Monkeys were housed and tested in stainless steel cages that measured 83.3 cm × 76.2 cm × 91.4 cm. Each cage was equipped with a response panel located on the left wall, approximately 10 cm from the front and 19 cm from the bottom of the cage. The panel contained three horizontally aligned levers, each of which could be activated by approximately 10-15 g of force. Three stimulus lights, each one of which was centered above a lever, were 2.5 cm in diameter and spaced 1.5 cm apart. Each light consisted of a circular opening that was covered with translucent plastic and capable of being illuminated from behind by 5-W colored bulbs.

Monkeys were implanted with an indwelling intravenous catheter that passed subcutaneously from the implanted vein to an exit site on the monkey's back. The catheter was fed through a stainless steel tether that was attached to the back of the Teflon mesh jacket (Lomir, Quebec, Canada) worn by each monkey. The other end of the tether was attached to the back wall of the cage. Once the catheter exited the tether at the rear of the cage, it ultimately was connected to three stock solutions, one with cocaine, one with remifentanil, and one with saline. The tubing that connected the catheter with each stock solution passed through an infusion pump (one per stock solution) which delivered 0.2 ml of solution per second. Each delivery lasted 5 s (totaling a 1-ml injection volume). Control of experimental sessions was provided by Med-PC (Med-Associates, Georgia, VT) interfacing and software (Version IV) installed on computers located in an adjacent room.

Procedure

Drug-dose selection. The monkeys in the present experiment were previously employed in an experiment conducted by Wade-Galuska, Winger, and Woods (2007). The doses selected for 3 of the monkeys in the present experiment (30 μg/kg/inf cocaine and 0.3 μg/kg/inf remifentanil) were based on data obtained by Wade-Galuska et al. that demonstrated that these doses maintained comparable levels of behavior across a variety of response requirements. When these doses were used in the choice phase of the present study, 2 of the 3 monkeys chose remifentanil nearly exclusively. Therefore, the 4th monkey (3506) was tested with a smaller dose of remifentanil (0.03 μg/kg/inf) so that the effects of morphine administration and deprivation could be observed in an animal that initially preferred cocaine.

Drug infusions. So that cocaine and remifentanil could be administered within the same session through the same catheter, the following procedure was employed: At the start of each session, approximately 1 ml saline was infused into the portion of the catheter external to the monkey (hereafter, the *external catheter*). During each reinforcer delivery, a 10-s infusion occurred consisting of two components. During the first component the drug pump operated for 5 s, pushing the saline (infused into the external catheter at the start of the session) into the monkey while filling the external catheter with 1 ml of the selected drug. The second component of an infusion consisted of the 5-s operation of the saline pump which pushed the drug into the monkey, while filling the external catheter with saline in preparation for the next reinforcer delivery.

Drug infusions were characterized by the same stimulus changes in all phases of the study. When an infusion was earned, the stimulus lights above the center and right levers were turned off and the light above the left lever turned green for the duration of the infusion. Following each infusion there was a 45-s timeout in which all stimuli were turned off and lever presses had no consequence.

Left-lever holding. This procedure, used in Wade-Galuska et al.'s 2007 experiment as well as in the present study, was implemented so that the monkeys could use only one hand, rather than pressing multiple levers, to select between the drug options. The procedure required that monkeys hold down the left lever (e.g., with the left hand) of the three-lever panel while completing a response requirement on another lever (e.g., with the right hand). At the start of a session, a white stimulus light above the left lever flashed (0.5 s on / off) until the left lever was pressed. Once the lever was pressed, the white stimulus light above the left lever stopped flashing (turning solid white) and the stimulus light above the operative lever turned to the color correlated with the drug associated with that lever. As long as the left lever was held down, responses on the operative lever counted toward completion of the response requirement. If the monkey stopped holding the left lever, the light above the operative drug lever was turned off and the white light above the left lever flashed until the left lever was again pressed. Releasing the left lever suspended the ongoing schedules, but did not reset the number of responses already made toward the ratio requirement.

Premorphine demand. The premorphine demand functions (demand functions obtained prior to daily morphine injections) for cocaine and remifentanil were reported in a previous study conducted by Wade-Galuska et al. (2007). The same general procedure was used to generate all demand functions reported in this experiment, including those obtained by Wade-Galuska et al. The response requirement was increased after every two consecutive sessions according to an ascending sequence of ratios: 10, 32, 100, 320, 562, and 1000. After this entire sequence of ratios was tested, two consecutive sessions at FR 10 followed by two consecutive sessions at FR 100 were conducted for each drug for replication purposes. During premorphine demand only, monkeys were exposed to a condition in which the center lever was the operative cocaine lever and another condition in which the right lever was the operative cocaine lever. Cocaine was correlated with a red stimulus light in both cases; a red light above the operative lever signaled that completion of the response requirement would result in a cocaine infusion. Demand also was assessed with remifentanil available for responding on either the center or right lever across conditions. Remifentanil was correlated with a blue stimulus light. Each drug was tested on each of the two levers to ensure that no lever biases existed for the center or right lever as the result of the left-lever holding procedure. No biases were observed, so these conditions were collapsed across lever-type in order to generate a single cocaine and remifentanil demand curve consisting of eight sessions at FR 10 and FR 100, and four sessions at the other ratios. The average consumption at each ratio was used in the creation of the premorphine demand curve. Once morphine injections began and throughout the remainder of the experiment, cocaine was associated with the center lever and remifentanil was associated with the right lever. Table 1 shows the order in which drugs were tested when generating demand functions before, during, and after daily morphine exposure. The order was counterbalanced

Table 1

Order in which drugs were tested in demand conditions occurring before (Pre), during (Daily), and following (Post) daily morphine administration.

Monkey	Drug (lever)	Condition		
		Pre	Daily	Post
3956	Coc (C)	1	2	–
	Coc (R)	4	–	–
	Remi (C)	3	–	–
	Remi (R)	2	1	–
3953	Coc (C)	2	1	1
	Coc (R)	1	–	–
	Remi (C)	4	–	–
	Remi (R)	3	2	2
2084	Coc (C)	2	2	1
	Coc (R)	1	–	–
	Remi (C)	4	–	–
	Remi (R)	3	1	2
3506	Coc (C)	1	1	2
	Coc (R)	2	–	–
	Remi (C)	3	–	–
	Remi (R)	4	2	1

across monkeys and across exposures within each monkey.

Premorphine choice. Following the completion of data collection for the experiment reported by Wade-Galuska et al. (2007) and immediately prior to the start of daily morphine injections, 30 μg/kg/inf cocaine and 0.3 μg/kg/inf remifentanil (or 0.03 μg/kg/inf remifentanil for Monkey 3506) were made available concurrently. Cocaine was available following the completion of an FR 10 schedule on the center lever and remifentanil was available following the completion of the same response requirement on the right lever. Under these circumstances, holding the left lever down turned on both the red stimulus light above the center lever and the blue light above the right lever allowing monkeys to respond for either drug. The FR 10 response requirement on one lever did not reset if a response(s) occurred on the other lever during the completion of a ratio. The response requirement for both drugs was reset only at the start of a new ratio following an infusion and subsequent 45-s timeout.

Choice sessions consisted of at least one lever reversal (two were conducted for Monkey 2084), during which remifentanil was earned from completing a ratio on the center lever and cocaine from completing a ratio on the right lever. The stimulus light color associated with each drug remained the same as it had been before. In all cases, preference tracked the reversal and choice was nearly identical to that observed prior to the reversal. A return to standard lever conditions (cocaine available on the right lever and remifentanil on the center) followed. Again, preference tracked this change. Behavior was judged stable (during the lever reversal and the return to standard lever conditions) when at least six sessions were conducted and when no increasing or decreasing trends in choice were observed. Only data from the last six sessions of the return to standard lever conditions were used in the calculation of premorphine choice.

Daily morphine administration. Once choice between cocaine and remifentanil was stable, daily injections of 3.2 mg/kg morphine began. Each injection was administered i.v. approximately 3 hr prior to the afternoon session and 20.5 hr prior to the session that occurred the following morning (recall that sessions were conducted twice daily, once in the morning and once in the afternoon). During the period of daily morphine administration, choice and demand data were analyzed separately for sessions occurring at the 3-hr and 20.5-hr time points.

Choice sessions continued while daily morphine injections were administered. Although not explicitly quantified, after about 2 weeks of morphine injections, one or more signs of mild withdrawal, including increased vocalization, salivation, and irritability, were observed prior to injections. These symptoms typically were alleviated upon the administration of morphine, indicating a mild degree of physical dependence on morphine. Monkeys also experienced some weight loss over the course of morphine administration. We concluded that this was likely due to morphine-induced decreases in food consumption rather than withdrawal-induced decreases in appetite because food consumption generally increased as the time since the most recent morphine injection increased (up to the time of the subsequent injection).

After at least 2 weeks and when choice was stable in sessions conducted at each time point, demand functions were again obtained for cocaine and remifentanil while daily morphine injections continued. Each ratio was in effect for two consecutive sessions as previously described, so that at least one session was conducted 3 hr after morphine and one session was conducted 20.5 hr after morphine at each response requirement. At least one response requirement (usually 10, 32, or 100) was then replicated. For the monkey (3506) that was tested with a small dose of remifentanil (0.03 μg/kg/inf) in choice sessions, the dose was increased to 0.3 μg/kg/inf because the smaller dose did not maintain behavior in the context of a demand procedure.

Postmorphine choice. Following daily morphine administration, Monkey 3956 became ill for reasons unrelated to the study, and was euthanized. The remaining monkeys were returned to the procedure that allowed them to choose between cocaine and remifentanil. The remifentanil dose was decreased to 0.03 μg/kg/inf for Monkey 3506 in order to compare preference before and after daily morphine administration. Also, Monkey 3953 experienced a catheter failure at the end of

Table 2

The average number of drug infusions earned over the last six stable choice sessions of each condition, including sessions prior to daily morphine (Pre), sessions occurring 3 and 20.5 hr following each morphine injection during daily morphine, and sessions conducted 4 to 5 weeks following daily morphine (Post). Standard deviation is shown in parentheses.

	Pre		3 hr		20.5 hr		Post	
Monkey	Coc	Remi	Coc	Remi	Coc	Remi	Coc	Remi
3956	20 (7)	83 (3)	22 (7)	20 (8)	4 (2)	86 (6)	–	–
3953	19 (7)	86 (3)	10 (4)	82 (7)	10 (3)	96 (3)	31* (5)	80* (3)
2084	34 (3)	48 (5)	44 (15)	15 (4)	14 (4)	101 (6)	48 (9)	54 (11)
3506	88 (2)	4 (3)	70 (9)	7 (8)	36 (10)	22 (7)	68 (7)	4 (3)

* Data based on choice sessions in which levers were reversed. See text for additional details.

daily morphine administration and had a 1-week hiatus and catheter implantation surgery prior to returning to the choice procedure. Once she resumed choice at the end of this hiatus, she responded exclusively for remifentanil. It is believed that this was because her most recent history was with remifentanil as the only drug available. Because of this, a lever reversal was conducted and stable choice (see Table 2), in which remifentanil was chosen at premorphine levels (as well as during daily morphine administration) was again observed.

Approximately 4 to 5 weeks later, demand was reassessed for each drug (see Table 1 for the order that drugs were tested) according to the demand procedure previously described.

All sessions lasted 2 hr and were conducted twice daily at the same times each day (once in the morning and once in the afternoon), 7 days per week.

Data Analysis

Demand curves. The exponential demand equation (Hursh & Silberberg, 2008) was fitted to the average number of drug deliveries earned at each response requirement. In this equation:

$$\log Q = \log(Q_0) + k\left(e^{-\alpha P} - 1\right),$$

Q represents the number of drug deliveries at each response requirement, or price (P). Q_0 is an estimate of consumption at zero-price and mathematically represents the y-intercept. The parameter k is a scaling parameter representing the range of the dependent variable in logarithmic units. We set k at a constant value of 3 for all analyses because it was the smallest whole number whose antilog (1000) was greater than all observed dependent values. The parameter α provides an index of elasticity of demand: As α increases, consumption drops off more quickly with increases in price. Conversely, smaller values of α reflect more inelastic functions in which consumption decreases more slowly with increases in price. Hursh and Silberberg argued that α provides a measure of the reinforcing effectiveness of a commodity. For instance, if opioid withdrawal increases the reinforcing effectiveness of a self-administered drug, the α parameter should decrease.

The graphing and statistical software Prism (GraphPad Software, Inc., San Diego, CA) was used in the graphing and statistical analysis of demand functions. We fitted the exponential demand function to the individual subject and group data for each drug and time point: pre, 3 hr, 20.5 hr, and post. In cases in which monkeys did not earn an injection, a value of 0.1 was assigned because the log of zero is undefined. We focused on two parameters of the exponential demand equation: α and Q_0. As described, α represents elasticity of demand. We also analyzed the Q_0 parameter as an index of the initial level of demand because it is possible that demand curves could shift vertically without affecting demand elasticity. For each drug, the values of these parameters, along with goodness of fit (R^2), were obtained both for the group and individually at each point of the study.

Response rate. Rates of responding were calculated for all sessions. However, the left lever-holding procedure used in the present experiment required that monkeys hold down the left lever in order to gain access to the schedule(s) in effect. Therefore, the time used in the calculation of response rate was incremented only when the left lever was

being held down. This time was not incremented during infusions or during the time spent in timeout following an infusion, when left-lever holding had no programmed consequences. Response rates were calculated as the number of responses divided by the adjusted session time. This procedure for calculating rates did not reflect the number of infusions earned during the demand procedure, although rates were congruent with choice in the choice procedure.

RESULTS

Choice

Table 2 shows the average number of remifentanil and cocaine infusions earned during stable choice sessions conducted before (pre), during, and following (post) daily morphine administration. Prior to the start of daily morphine injections, 3 of the 4 monkeys showed a preference for remifentanil, although Monkey 2084 chose remifentanil much less relative to the other monkeys (approximately 60% versus 80%; see Figure 1, unconnected data points above first sessions) exhibiting this preference. In an attempt to evaluate the study parameters in a monkey that initially preferred cocaine, the remifentanil dose for Monkey 3506 was smaller: 0.03 g/kg/inf. Under these conditions, this monkey showed a near- exclusive preference for cocaine.

During the period of daily morphine injections, choice of remifentanil varied across monkeys in the sessions conducted 3 hr following injections (left panels, Figure 1). Monkeys 3956 and 2084 both showed about a 50% decrease in their choice of remifentanil and a corresponding increase in their choice of cocaine. However, this change in choice was abrupt for Monkey 2084 and more gradual for 3956. Monkey 3953 showed an initial decrease in choice of remifentanil from 80% to 60% over the first 2 days of morphine administration. Thereafter, choice of remifentanil recovered to premorphine levels. Choice of a smaller dose of remifentanil remained at premorphine levels (near-zero) for Monkey 3506.

Premorphine response rates reflected preference: The remifentanil-preferring monkeys responded more rapidly for remifentanil compared to cocaine (Monkey 2084 responded just slightly faster for remifentanil) whereas the cocaine-preferring monkey (3506) responded more rapidly for cocaine than for remifentanil (right panels, Figure 1). Response rates maintained by cocaine increased 3 hr following morphine administration for Monkeys 3956, 2084, and 3506, although rates eventually returned to premorphine levels for Monkey 2084 by the time stable behavior was observed. Rates of remifentanil-maintained responding decreased, with the exception of Monkey 3506 whose rates generally did not change relative to premorphine rates. This likely was due to a floor effect that resulted from the low dose of remifentanil self-administered by this monkey during the assessment of choice.

Figure 2 shows choice of remifentanil and response rates for remifentanil and cocaine in the sessions that occurred 20.5 hr following each morphine injection. Choice of remifentanil (relative to cocaine) increased for all monkeys with the exception of Monkey 3953, whose preference for remifentanil remained unchanged relative to premorphine. Whereas Monkey 3506 did not develop a preference for remifentanil as the result of daily morphine exposure, he did consume more remifentanil than in the premorphine condition (during which he chose cocaine almost exclusively). Response rates for remifentanil increased over the course of morphine administration for Monkeys 3956, 2084, and 3506. Concurrently, rates of responding for cocaine decreased for Monkeys 3956 and 2084. Monkey 3953's rates did not change appreciably for either drug.

Following evaluation of demand (results below), daily morphine injections were discontinued and the remaining monkeys were again allowed to choose between cocaine and remifentanil. The number of injections of each drug in stable postmorphine choice sessions is shown in Table 2. For the most part the pattern of choice returned to premorphine levels. The number of overall injections increased slightly for Monkey 2084, whereas the number of cocaine injections was elevated relative to previous conditions for Monkey 3953 and remained low relative to premorphine conditions for Monkey 3506.

Demand

For each monkey and time point, the mean numbers of infusions earned at each response

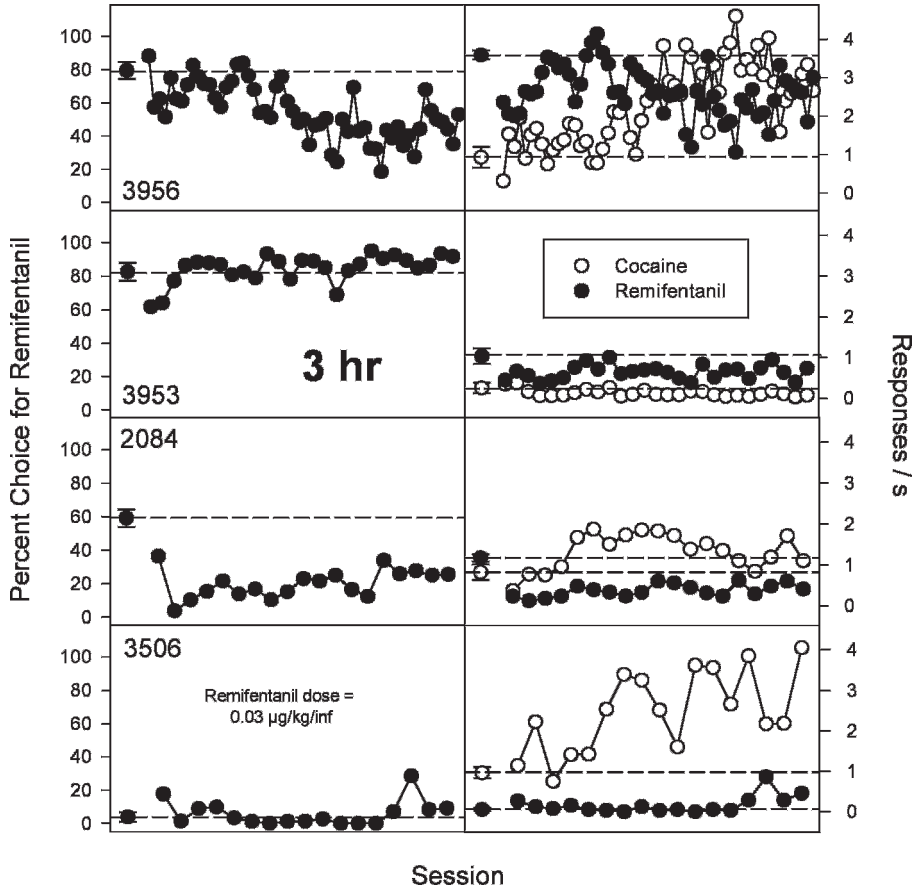

Fig. 1. Choice between a dose of remifentanil and a dose of cocaine 3 hr after daily administration of 3.2 mg/kg/inj morphine in 4 rhesus monkeys. Percent choice of remifentanil is shown on the left ordinate and rates of responding maintained by the doses of remifentanil and cocaine are shown on the right ordinate. The initial data point and the horizontal dashed line represent premorphine choice; the error bars are standard deviations. Daily sessions are shown on the abscissa. Note that the dose of remifentanil is 0.03 µg/kg/inj for Monkey 3506 (bottom) and 0.3 µg/kg/inj for the other monkeys.

requirement are shown in Tables 3 (cocaine) and 4 (remifentanil). Shown in parentheses are the average response rates (responses/s). Figure 3 shows the group mean number of cocaine (top panel) and remifentanil (bottom panel) infusions earned as a function of the response requirement on a log–log scale at each time point.

For each drug, the exponential demand equation (Hursh & Silberberg, 2008) then was fitted separately to the data from each time point. Obtained α, Q_0, and goodness-of-fit (R^2) values are shown in the Group section of Table 5. Also shown in Table 5 are the same parameters obtained when the exponential demand equation was fitted to the individual subject infusion data for each drug and time point. With respect to cocaine demand, the Q_0 parameter—representing an estimate of consumption at zero-price—was higher for each monkey in the 20.5-hr and postmorphine time periods relative to the premorphine period. The Q_0 parameter also was higher in the 3-hr period relative to the premorphine period for 3 of 4 monkeys. With respect to the α parameter, for each monkey the postmorphine demand curve was more inelastic than the premorphine demand curve, as indicated by lower α values. In 3 of 4 monkeys, demand curves obtained at the 20.5-hr time points also

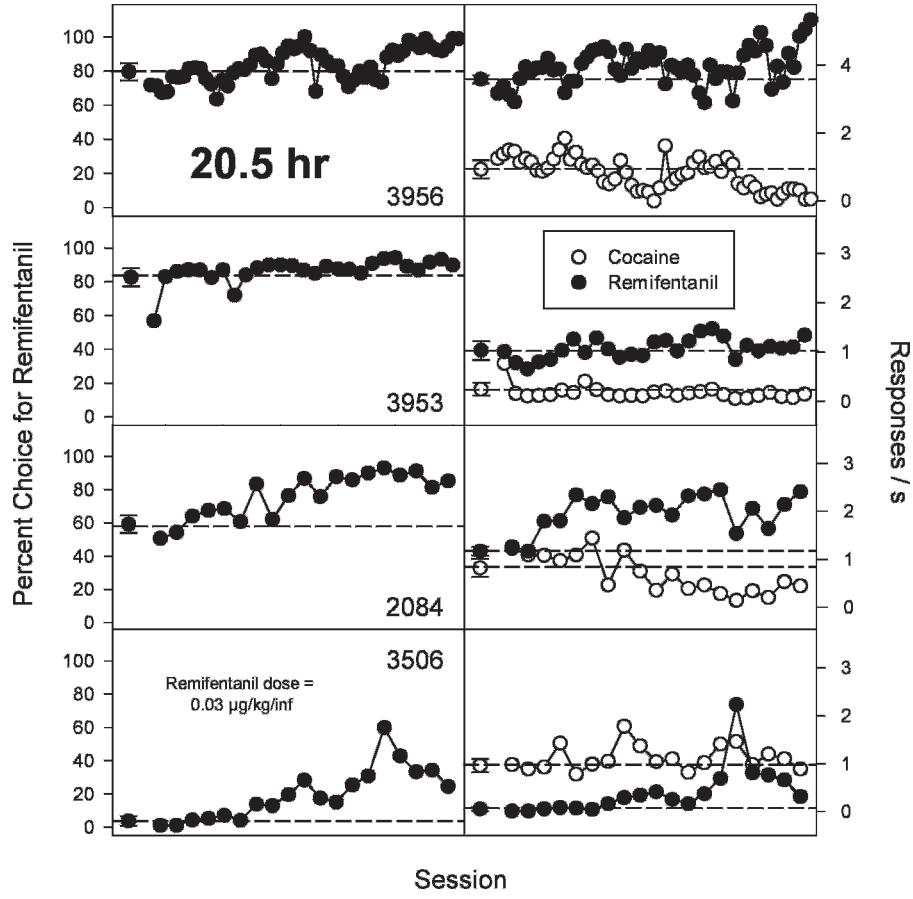

Fig. 2. Choice between a dose of remifentanil and a dose of cocaine 20.5 hr after daily administration of 3.2 mg/kg/inj morphine in 4 rhesus monkeys. Percent choice of remifentanil is shown on the left ordinate and rates of responding maintained by the doses of remifentanil and cocaine are shown on the right ordinate. The initial data point and the horizontal dashed line represent premorphine choice; the error bars are standard deviations. Daily sessions are shown on the abscissa. Note that the dose of remifentanil is 0.03 µg/kg/inj for Monkey 3506 (bottom) and 0.3 µg/kg/inj for the other monkeys.

were more inelastic relative to the premorphine curves. Demand elasticity 3-hr postmorphine resembled that obtained premorphine.

Examination of the individual subject data in Table 5 also shows that with respect to remifentanil demand, the Q_0 parameter was lower for each monkey at the 3-hr time period relative to the premorphine period. In addition, 3 of 4 monkeys exhibited enhanced Q_0 parameters 20.5 hr after a morphine injection relative to the premorphine demand curve. The Q_0 parameter obtained postmorphine was slightly lower than that obtained premorphine for each monkey.

Relative to the premorphine demand curve, the remifentanil demand curve obtained at the 3-hr time period was more elastic (higher α values) for each monkey. Three of four monkeys exhibited less elastic demand functions 20.5 hr after a morphine injection relative to that obtained premorphine. Finally, 2 of 3 monkeys continued to exhibit less elastic demand functions during the postmorphine determination relative to the premorphine determination.

Figure 4 shows the group demand curves for cocaine and remifentanil at each time period. These demand curves are the same curves as presented in Figure 3, but here they are grouped by time period for the purposes of additional comparisons. In the premorphine baseline, cocaine demand was more elastic

Table 3

The average number of infusions and response rate (responses/s; shown in parentheses) associated with demand for cocaine prior to daily morphine (Pre), 3 and 20.5 hr following each morphine injection during daily morphine, and 4 to 5 weeks following daily morphine (Post).

Monkey	FR	Pre	3 hr	20.5 hr	Post
3956	10	74 (3.2)	92 (5.6)	81 (1.3)	–
	32	41 (3.0)	69 (5.6)	90 (5.4)	–
	100	22 (2.8)	20 (5.4)	49 (5.8)	–
	320	2 (1.6)	1 (5.6)	9 (6.2)	–
	562	0 (1.2)	0 (3.6)	0 (3.1)	–
	1000	0 (0.9)	0 (4.0)	0 (5.2)	–
3953	10	80 (1.8)	96 (1.4)	99 (1.3)	115 (2.0)
	32	46 (2.3)	67 (1.7)	78 (1.4)	99 (2.3)
	100	34 (2.5)	27 (1.1)	29 (1.8)	38 (2.4)
	320	16 (1.8)	2 (0.3)	10 (2.2)	11 (2.3)
	562	5 (1.4)	0 (0.1)	2 (2.6)	7 (2.6)
	1000	0 (0.7)	0 (0.1)	0 (1.2)	1 (1.0)
2084	10	87 (1.5)	47 (1.9)	111 (1.7)	112 (2.4)
	32	79 (1.8)	33 (2.3)	109 (4.2)	91 (3.9)
	100	48 (2.8)	24 (1.6)	93 (5.2)	70 (4.6)
	320	14 (2.3)	23 (2.2)	54 (4.6)	23 (4.3)
	562	2 (1.3)	2 (1.0)	32 (4.2)	17 (4.6)
	1000	0 (0.6)	8 (1.6)	16 (4.6)	2 (5.6)
3506	10	62 (2.2)	57 (1.5)	60 (1.0)	88 (1.1)
	32	44 (2.4)	44 (2.6)	71 (1.6)	67 (1.5)
	100	27 (2.1)	43 (1.7)	37 (2.4)	38 (2.1)
	320	12 (2.4)	0 (1.5)	23 (2.8)	22 (2.8)
	562	7 (2.4)	0 (0.9)	11 (3.2)	6 (2.5)
	1000	1 (2.1)	0 (1.0)	4 (2.8)	1 (1.6)

Table 4

The average number of infusions and response rate (responses/s; shown in parentheses) associated with demand for remifentanil prior to daily morphine (Pre), 3 and 20.5 hr following each morphine injection during daily morphine, and 4 to 5 weeks following daily morphine (Post).

Monkey	FR	Pre	3 hr	20.5 hr	Post
3956	10	85 (3.8)	17 (3.3)	91 (4.2)	–
	32	51 (3.7)	2 (2.8)	72 (5.0)	–
	100	17 (3.5)	0 (4.0)	38 (6.0)	–
	320	4 (3.3)	0 (2.4)	5 (5.9)	–
	562	2 (2.9)	0 (4.4)	0 (4.1)	–
	1000	0 (2.4)	0 (4.6)	0 (2.1)	–
3953	10	92 (0.7)	30 (0.2)	68 (0.6)	92 (0.8)
	32	72 (1.2)	28 (0.4)	64 (1.1)	59 (0.7)
	100	43 (1.5)	5 (0.3)	36 (1.4)	33 (0.9)
	320	17 (1.9)	0 (0.2)	17 (3.1)	13 (1.5)
	562	8 (2.2)	0 (0.0)	3 (2.6)	7 (2.2)
	1000	3 (1.6)	0 (0.0)	1 (3.1)	3 (2.6)
2084	10	76 (0.7)	65 (0.2)	95 (0.7)	84 (0.5)
	32	67 (1.3)	46 (0.4)	89 (1.5)	74 (0.9)
	100	46 (1.9)	31 (0.7)	72 (2.5)	53 (1.5)
	320	20 (2.7)	9 (0.8)	44 (4.0)	31 (2.8)
	562	7 (3.2)	8 (1.0)	30 (3.9)	23 (3.2)
	1000	2 (2.7)	0 (0.4)	4 (2.5)	13 (3.7)
3506	10	73 (1.4)	30 (0.8)	99 (2.2)	66 (1.9)
	32	58 (1.5)	17 (0.8)	87 (2.3)	57 (2.1)
	100	31 (2.4)	4 (1.4)	65 (2.7)	42 (2.0)
	320	14 (2.7)	4 (0.5)	35 (3.0)	23 (2.4)
	562	6 (2.7)	0 (0.0)	21 (3.1)	13 (2.3)
	1000	2 (2.7)	0 (3.3)	7 (3.7)	5 (2.8)

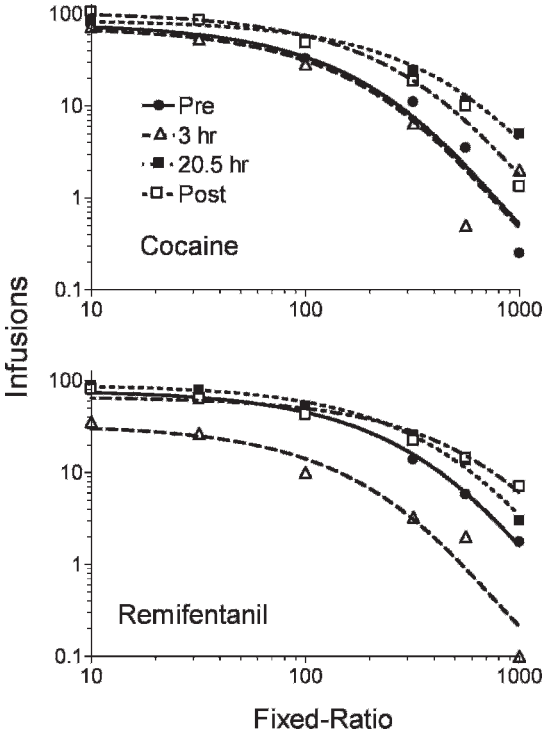

Fig. 3. Group demand curves for cocaine (top) and remifentanil (bottom) prior to morphine administration (closed circles, solid lines), 3 hr after daily morphine (open triangles, dashed lines), 20.5 hr after daily morphine (closed squares, dotted lines), and 4 to 5 weeks following termination of daily morphine (open squares, dotted-dashed lines). Data points represent the group means.

(higher α values) than remifentanil demand for each. There were no consistent differences in the Q_0 parameter between cocaine and remifentanil at this time point.

Three hours after a morphine injection, the relative elasticity of cocaine and remifentanil reversed. During this period, remifentanil demand was more elastic than cocaine demand for each monkey. In addition, for 3 of 4 monkeys, the Q_0 value associated with the cocaine demand curve was higher than that associated with the remifentanil demand curve.

At 20.5 hr after a morphine injection and during the postmorphine determination, the Q_0 parameter associated with cocaine usually was higher than that of remifentanil for each monkey except Monkey 3506 (20.5-hr period). There were no consistent between-drug differences in α at the 20.5-hr time point. Similar to the premorphine period, cocaine demand was more elastic than remifentanil demand in 2 of 3 monkeys during the postmorphine determination.

DISCUSSION

The present study investigated two methods for measuring changes in the reinforcing effectiveness of remifentanil in opioid-dependent monkeys. The first allowed monkeys to choose between remifentanil and cocaine. The second reflected changes in demand for both drugs. Using both procedures, there was some evidence that the reinforcing effect of remifentanil was enhanced during withdrawal (20.5 hr after a morphine injection). First, monkeys exhibited increased choice of remifentanil over cocaine in the choice procedure during this time. In addition, for 3 of 4 monkeys, demand became more inelastic (lower α values) and the initial level of demand (Q_0) increased. Interestingly, demand for cocaine also tended to increase during morphine withdrawal, as illustrated by lower α values and higher Q_0 values in most monkeys (3 of 4 and 4 of 4, respectively).

The results from the choice and demand procedures are mostly congruent. In the premorphine baseline, the 3 monkeys self-administering 0.3 μg/kg/infusion remifentanil preferred remifentanil to cocaine. For these monkeys, demand for remifentanil also was more inelastic relative to cocaine. Three hours after a morphine injection, 2 of the 3 monkeys self-administering 0.3 μg/kg/infusion remifentanil (Monkey 3953 being the exception) showed individual patterns of choice that generally indicated a decrease in the relative reinforcing effects of remifentanil or an increase in the relative reinforcing effects of cocaine. Parallel results are seen in the demand curves obtained at this time point; demand for remifentanil became more elastic relative to cocaine. A selective decrease in opioid self-administration engendered by opioid administration has been demonstrated in monkeys responding for food or drug in other situations (e.g., Mello, Bree, & Mendelson, 1983; Winger & Woods, 2001) and may be a general effect of this drug class. An exception to this general pattern are the choice results from Monkey 3953. For this monkey, choice appeared quite insensitive to the effects of

Table 5

Parameters describing demand for cocaine and remifentanil in conditions prior to daily morphine injections (Pre), 3 and 20.5 hr following each morphine injection during daily morphine, and 4 to 5 weeks following daily morphine (Post). The Group parameters correspond to the demand curves shown in Figures 3 and 4.

		Cocaine				Remifentanil			
Monkey	Measure	Pre	3 hr	20.5 hr	Post	Pre	3 hr	20.5 hr	Post
3956	Q_0	85.8	121.2	132.6	—	70.7	57.6	123.6	—
	α	3.62E-5	3.30E-5	2.03E-5	—	2.47E-5	3.78E-4	2.37E-5	—
	R^2	.94	.97	.83	—	.95	.99	.88	—
3953	Q_0	80.4	121.0	100.6	106.6	79.8	55.5	77.1	66.6
	α	1.69E-5	2.86E-5	1.75E-5	1.01E-5	8.67E-6	9.73E-5	1.30E-5	1.00E-5
	R^2	.87	.94	.94	.97	.98	.96	.98	.96
2084	Q_0	109.5	35.2	114.6	116.7	79.7	69.6	109.9	73.1
	α	1.57E-5	1.15E-5	3.01E-6	6.64E-6	9.50E-6	1.84E-5	4.91E-6	4.26E-6
	R^2	.92	.54	.99	.96	.99	.84	.93	.96
3506	Q_0	56.0	104.8	64.5	88.0	63.9	26.1	96.2	62.4
	α	1.40E-5	4.85E-5	8.07E-6	1.06E-5	1.14E-5	1.50E-5	4.89E-6	7.39E-6
	R^2	.97	.81	.98	.98	.99	.84	.99	.99
Group	Q_0	78.8	72.1	85.6	104.1	78.1	32.9	89.7	66.3
	α	1.65E-5	1.81E-5	6.67E-6	8.58E-6	1.06E-5	3.99E-5	7.14E-6	6.42E-6
	R^2	.96	.79	.99	.98	1.00	.94	.99	.97

morphine either 3 hr or 20.5 hr following its administration. Despite minimal effects on choice, following morphine administration, demand for remifentanil appeared to be more suppressed than demand for cocaine in this monkey, as indexed by lower Q_0 values and higher α values.

When monkeys were displaying signs of mild opioid withdrawal, all monkeys except Monkey 3953 showed a gradually increasing choice of

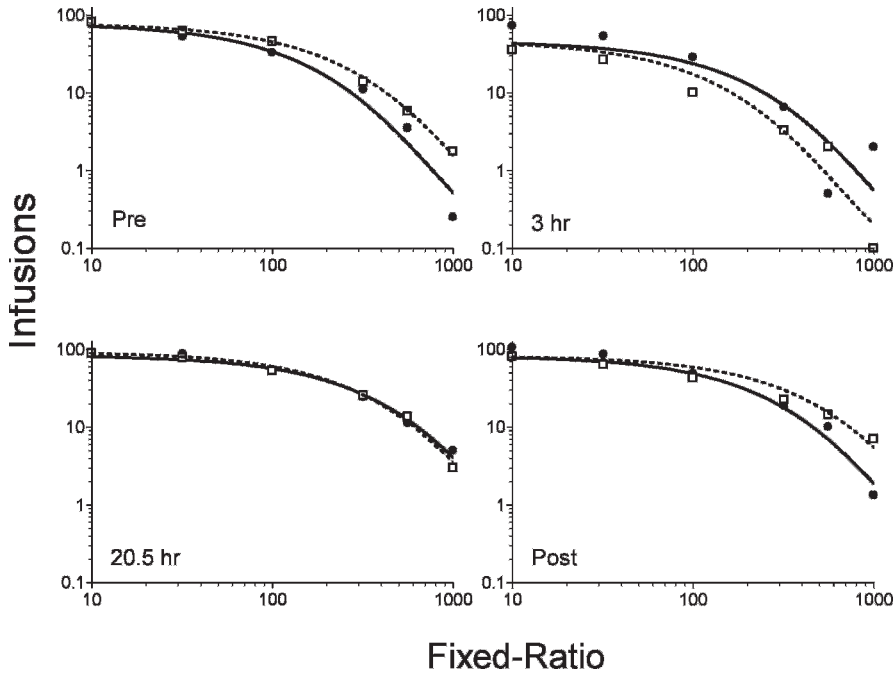

Fig. 4. Group demand curves for cocaine (closed circles, solid lines) and remifentanil (open squares, dotted lines) at each time point. Data points represent the group means.

remifentanil 20.5 hr following daily morphine injections. Interestingly, Monkey 3953 was the only monkey for whom demand for remifentanil became more elastic (relative to the premorphine period). Thus, in 3 of 4 monkeys, both measures of the reinforcing effects of remifentanil indicated that remifentanil became a better reinforcer relative to cocaine during mild opioid withdrawal. In addition, demand for cocaine also increased (lower α values and higher Q_0 values) relative to cocaine demand prior to morphine exposure. The finding that cocaine demand increased during morphine withdrawal might be unexpected, particularly because choice for cocaine over remifentanil was decreased at this time. However, it is consistent with the finding of Gerak et al. (2009) that responding maintained by small doses of cocaine was increased 17 hr following the discontinuation of morphine. In the context in which it is the only drug available, it is possible that cocaine becomes a better reinforcer during opioid withdrawal than it is in the absence of withdrawal. Indeed, previous research in our laboratory has demonstrated that cocaine and remifentanil are economic substitutes (Wade-Galuska et al., 2007). As such, operations that increase the reinforcing effectiveness of remifentanil also should increase the reinforcing effectiveness of cocaine. Cocaine, however, appears to be an imperfect substitute for remifentanil. When remifentanil was concurrently available in the choice procedure, the relative reinforcing effectiveness of cocaine was lower than that of the opioid.

It is also possible that the increase in cocaine demand during opioid withdrawal could be attributed to the conditioned reinforcing functions of the stimuli associated with drug infusions. Although the discriminative light stimuli for cocaine and remifentanil availability were different in color, the light that accompanied infusions of both drugs was the same color and location. Therefore, observed demand for cocaine during morphine withdrawal could be, at least in part, demand for the stimuli previously paired with remifentanil.

Demand for stimuli paired with drug reinforcers has not been evaluated explicitly, although such measurement might be helpful as a quantitative index of drug craving (Weiss, 2005). In the current situation where there is a confound between cocaine delivery and stimuli paired with remifentanil delivery, the precise nature of the stimuli maintaining behavior cannot be specified. Nevertheless, the data indicate that polydrug abusers may show increased intake of a stimulant during opioid withdrawal, particularly when the setting conditions for administration of the two drugs are similar.

One difficulty with comparing drugs in a choice paradigm is that preference depends on the dose of each drug compared. The doses of cocaine and remifentanil used here were chosen on the basis of previous research (Wade-Galuska et al., 2007) showing that they resulted in comparable levels of responding in the context of a demand procedure. Prior to the start of daily morphine administration it would have been ideal for the monkeys to respond about equally for both drugs, providing a baseline that could easily detect increases or decreases in preference for either drug as the result of morphine exposure. In the present study, however, preference for remifentanil was observed for 3 of the 4 monkeys, with choice being nearly exclusive for two of them. The fourth monkey showed a preference for cocaine due to the fact that a smaller dose of remifentanil was used. It is likely that exclusive or nearly exclusive choice for one of the drugs was demonstrated because an FR schedule of reinforcement was used. FR schedules tend to favor exclusive preference for the alternative that is available at a cheaper price or that is more favorable. For this reason it is unlikely that any doses would have resulted in indifference between these drugs.

While the results from the choice and demand assays are mostly congruent, in some respects it appears as if the choice procedure may be better at revealing differences in the reinforcing effects of drugs than the analysis of demand. Consider that there was no consistent difference between the Q_0 parameter between drugs during the premorphine baseline. At the smallest price investigated (FR 10), consumption of the two drugs was comparable. Nevertheless, at the same price, near-exclusive preference was obtained for remifentanil. In addition, choice of remifentanil increased relative to cocaine at the 20.5-hr time point, but elasticity of demand for both drugs at this time point were virtually identical (Figure 4, lower left). Thus, it appears that the choice procedure appears to be exquisitely sensitive

to the relative reinforcing effectiveness of the two drugs. Nevertheless, choice procedures do not provide a measure of absolute reinforcing effectiveness. According to Hursh and Silberberg (2008), measures of demand eliminate the influence of alternatives on the consumption of a commodity and therefore provide a more absolute measure of what they refer to as essential value. In the case of choice and demand at the 20.5-hr time point, while the relative reinforcing value of remifentanil was increased, the absolute reinforcing value of cocaine also increased, probably due to its substitutability with remifentanil. Thus, investigating both choice and demand provides a more complete picture of how morphine withdrawal modulates the reinforcing value of these two drugs than either measure alone.

The changes in demand for remifentanil and the changes in preference for remifentanil were not large in this study. This was perhaps due to the fact that the dose of morphine given daily, 3.2 mg/kg/day, was fairly small. Although this dose is sufficient to produce opioid receptor antagonist-generated withdrawal-induced discriminative-stimulus effects in monkeys (France & Woods, 1989) and tolerance to the reinforcing effects of low efficacy agonists (Winger & Woods, 2001), the withdrawal signs produced by the termination of the morphine dose in the present study were small relative to those produced by large doses of heroin or morphine administered in some previous studies (Negus, 2006; Griffiths et al. 1981; Gerak et al. 2009). A larger dose of morphine, or twice-daily administration of the current dose, would have produced much more intense withdrawal signs that likely would have magnified the relatively small changes in choice and demand that were observed in this study. Nevertheless, it is interesting and important to observe that changes in preference for an opioid can occur even under conditions of very mild opioid withdrawal.

Following the conclusion of morphine injections, choice of remifentanil and cocaine approximated what was observed prior to morphine administration. However, demand for cocaine and remifentanil remained inelastic relative to the premorphine condition in most cases (the results of remifentanil demand for Monkey 3953 is the only exception). This suggests the possibility that withdrawal-associated increases in the reinforcing effectiveness of these drugs lasted beyond (in this case 4 to 5 weeks after) the period of dependence. Prolonged withdrawal has been observed using cardiovascular measures in rhesus monkeys up to 3 weeks after discontinuation of 5.6 mg/kg morphine twice daily (Becker, Gerak, Koek, & France, 2008). Gerak et al. (2009) reported increases in responding by rhesus monkeys for very small doses of heroin up to 10 weeks after withdrawal of 10 mg/kg morphine twice daily, and Zhou et al. (2004) noted increased responding for the stimuli previously associated with heroin in rats 4 weeks after heroin self-administration was discontinued.

Unfortunately, in this study it was not possible to determine if the long-term changes in elasticity observed are due solely to the morphine regimen. The results are confounded by a history of continued drug self-administration. Christensen, Silberberg, Hursh, Roma, and Riley (2008) demonstrated that rats' demand for cocaine became more inelastic simply by providing a continued history of cocaine self-administration. Nevertheless, if the reinforcing effectiveness of an opioid drug is enhanced even when physical symptoms of withdrawal are no longer apparent—for whatever reason—this may contribute to relapse in recovering dependent individuals. It is worth determining whether a similar enhancement of the reinforcing effectiveness of stimulants, which produce little or no physical withdrawal, occurs following administration of large doses of drugs of the stimulant class.

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Received: September 11, 2009
Final Acceptance: October 23, 2010