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Delay discounting of food and remifentanil in rhesus monkeys

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Abstract

Rationale Drug abuse can be conceptualized as choice between drug and non-drug reinforcers in which drug choice is excessive; factors impacting drug taking can be examined using procedures in which subjects choose between drug and an alternative reinforcer. **Objective** This experiment examined the effects of delayed reinforcement on choice between food and the mu opioid receptor agonist remifentanil. **Methods** Rhesus monkeys responded under a concurrent fixed-ratio 5, fixed-ratio 5 schedule in which responding on one lever delivered one food pellet and responding on another lever delivered an i.v. infusion. **Results** With no delay, monkeys responded predominantly for food rather than saline or small doses of remifentanil; as the dose of remifentanil increased (0.1–1.0 $\mu\text{g/kg/infusion}$) monkeys responded more for drug. Delaying delivery (30–240 sec) of 0.32 but not 1.0 $\mu\text{g/kg/infusion}$ of remifentanil (food delivered immediately) decreased responding for drug and increased responding for food, resulting in a rightward shift in the remifentanil dose-effect curve. Delaying delivery of food (60–240 sec) when doses of remifentanil smaller than 0.32 $\mu\text{g/kg/infusion}$ (but not saline) were available decreased responding for food and increased responding for drug, resulting in a leftward shift in the remifentanil dose-effect curve. **Conclusion** These results provide evidence that delaying the delivery of a mu opioid receptor agonist reduces its potency as a positive reinforcer; more importantly, delaying the delivery of an alternative non-drug reinforcer (e.g., food) enhances the reinforcing potency of the agonist. Thus, understanding the factors that control substance abuse requires examination of contingencies for both drug and non-drug reinforcers.

Keywords

delay discounting; food; choice; remifentanil; opioid; rhesus monkey

Introduction

Drug abuse remains a significant public health problem; in particular, opioid abuse (e.g., prescription opioids) has increased in the past decade among adolescents and young adults (e.g., Compton and Volkow 2006; Johnston et al. 2012). Many variables contribute to the development and maintenance of drug taking, and an understanding of these factors will aid both in the identification of risk factors and the development of better treatments. Drug abuse can be conceptualized as choice between drug and non-drug reinforcers in which drug choice is excessive (e.g., Heyman 2009), and factors that impact drug choice have been studied using procedures in which subjects choose between drug and non-drug reinforcers (see Negus and Banks 2011 for a recent review). When drug abuse is conceptualized as

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choice, two general classes of controlling variables appear to impact drug taking: the availability (e.g. cost, quality, magnitude) of drug and the availability of alternative reinforcers. Whether an individual engages in drug taking depends upon the interaction between these two classes of variables, and choice procedures are ideal for elucidating these relationships (e.g., Paronis et al. 2002; Negus 2003).

Within these two classes of variables, there are a number of factors associated with delivery of the drug or alternative non-drug reinforcers. For example, increasing the response requirement for delivery of cocaine or decreasing the response requirement for delivery of the alternative reinforcer (e.g., food), decreases responding for cocaine and increases responding for an alternative reinforcer (e.g., Nader and Woolverton 1992; Negus 2003). Altering the magnitude of drug (i.e., dose) or the alternative (e.g., number of food pellets) also can impact drug taking (e.g., Nader and Woolverton 1991; Campbell and Carroll 2000; Negus 2003). Consistent with results of studies with nonhuman species, studies with humans show that drug taking is similarly influenced by the magnitude, type, and availability of drug and non-drug reinforcers (e.g., Higgins 1997).

Another factor that can impact choice is the temporal relationship between a response and delivery of the reinforcer (i.e., delay). When given a choice between immediate and delayed delivery of a reinforcer, subjects reliably choose immediate delivery (c.f., Chung and Herrnstein 1967), demonstrating that preference for a reinforcer can be reduced by delaying its delivery. This process is known as delay discounting (e.g., Mazur, 1987), and individual differences in delay discounting might predispose individuals toward certain behavioral patterns. For example, individuals who discount delayed reinforcers more rapidly might be more inclined to choose the more immediately available consequences of drug taking (e.g., drug effects) rather than the delayed consequences of remaining abstinent (e.g., health, income, and positive social relationships). Preference for small, immediately available reinforcers over larger, delayed reinforcers is thought to reflect a greater degree of impulsivity or lack of self-control (Rachlin, 1974; Ainslie 1975; Logue 1988). Drug abuse is often characterized as a disorder of impulse control, and current drug users discount delayed reinforcers more rapidly than individuals who have never used drugs or those who are drug abstinent (e.g., see reviews by Bickel and Marsch, 2001; Perry and Carroll, 2008; de Wit and Mitchell, 2010). Moreover, drug-dependent individuals tend to discount drugs more rapidly than non-drug reinforcers of equivalent value (e.g., Madden et al. 1997), suggesting that the type of (delayed) reinforcer impacts the rate of discounting.

Delaying reinforcement can significantly modulate drug-maintained behavior in rhesus monkeys. For example, in monkeys responding under a single-response i.v. self-administration procedure, imposing a delay between completion of the fixed-ratio requirement and delivery of cocaine decreased response rates (Beardsley and Balster 1993). When choosing between 0.01 mg/kg/infusion of cocaine delivered immediately and 0.03 mg/kg/infusion of cocaine delivered after a delay, responding for the smaller dose of cocaine increased as the delay to the larger dose increased (e.g., Woolverton et al. 2007). Similarly, when given a choice between food and a dose of cocaine that maintained exclusive responding when both were delivered immediately, delaying delivery of drug decreased responding for cocaine and increased responding for food, indicating that responding is sensitive to delay when monkeys chose between cocaine and food (Woolverton and Anderson 2006).

The current study examined the impact of magnitude of drug reinforcement (i.e., dose) on delay discounting in rhesus monkeys responding under a drug-versus-food choice procedure. During daily sessions, monkeys could choose between food and an i.v. infusion of the mu opioid receptor agonist remifentanyl. The delay to delivery of either food or drug was

manipulated systematically, generating delay curves for each reinforcer. Remifentanyl was chosen for this study because, like other μ opioid receptor agonists (e.g., heroin), it is readily self-administered by non-human primates. Its fast onset and short duration of action (as compared to heroin) make it ideal to study under conditions in which monkeys can make repeated choices by minimizing the likelihood of encountering effects that result from accumulation of drug over the course of repeated infusions (e.g., response rate suppression).

Materials and Methods

Animals

Three adult rhesus monkeys (*Macaca mulatta*), two female (MA and GA) and one male (EL), were used in this study. ME and GA previously discriminated 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (Li et al. 2008); these monkeys had limited experience (less than 30 sessions with up to 30 infusions per session) lever-pressing for cocaine (0.032 μ g/kg/infusion). EL was experimentally naïve. Body weight (7-9 kg) was maintained by post-session feeding (Harlan Teklad, High Protein Monkey Diet, Madison, WI, USA). Monkeys received fresh fruit and peanuts daily; water was continuously available in home cages. Subjects were housed individually under a 14/10-hour light/dark cycle. Animals used in these studies were maintained in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center at San Antonio, and the 2011 Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animals Resources on Life Sciences, National Research Council, National Academy of Sciences).

Apparatus

During sessions, subjects were seated in commercially available chairs (Model R001; Primate Products, Miami, FL) located in ventilated, sound-attenuating chambers. Response panels in each chamber contained 2 retractable levers (Model ENV-612M, Med Associates, Inc., Georgia, VT) and 3 horizontally aligned green lights. Food reinforcement consisted of one 300-mg banana flavored food pellet (Bio-Serv Dustless Precision Pellets, F0179) delivered from a pellet dispenser (Model ENV-203-300, Med Associates) to a food receptacle located below the center light. Drug and saline were delivered by a vascular access port (Access Technologies, Skokie, IL) connected to a 185-cm extension set (Abbott Laboratories, Stone Mountain, GA) via a 20-g Huber-point needle (Access Technologies). A 30-ml syringe was mounted in a syringe driver (Model PHM-100, Med Associates) that infused at a rate of 2.3 ml/min. An interface (Med Associates) and a PC-compatible computer controlled experimental events and recorded data.

Surgery

Monkeys were anesthetized with 10 mg/kg of ketamine (Fort Dodge Laboratories, Fort Dodge, IA) prior to intubation, and anesthesia was maintained by isoflurane (Butler Animal Health Supply, Grand Prairie, TX); oxygen was delivered at 2 l/min. A catheter (5 Fr, PolyFlow polyurethane, SIMS Deltec) was implanted in the jugular or femoral vein, tunneled subcutaneously to the midscapular region of the back, and connected to the vascular access port.

Procedures

Sessions, conducted 7 days per week and lasting approximately 100 min, began with 2 forced trials followed by 10 choice trials. Monkeys were presented with all choice trials each session, regardless of performance. All features of the forced trials (e.g., response requirement, dose, delay, and stimuli) were identical to choice trials of that session except that only one lever was extended and only the green light located above that lever was

illuminated. Five responses retracted the lever, extinguished the light, and delivered the reinforcer (food pellet or infusion) that was associated with responding on that lever during the subsequent choice trials of that session. During the second forced trial, the other lever was extended and the green light above that lever was illuminated. Five responses on that lever retracted the lever, extinguished the light, and delivered the alternative reinforcer. The order of presentation of forced trials varied quasi-randomly across sessions with the constraint that the same order did not occur for more than 2 consecutive sessions. During choice trials, both levers were extended with green lights illuminated above each lever. Five consecutive responses on either lever immediately retracted both levers, extinguished both lights, and delivered the reinforcer associated with that lever. Responses on either lever reset the ratio requirement on the other lever. If a reinforcer was delivered immediately, the center white light flashed for 0.2 sec followed by reinforcer delivery. If reinforcer delivery was delayed, the center white light was illuminated for the duration of the delay and extinguished when the food pellet was delivered or the infusion was initiated. No lights were present during the infusion or the subsequent blackout period. There was no limited hold for forced trials; both forced trials had to be completed prior to initiating the choice trials. During choice trials, failure to satisfy the response requirement within 30 sec was a trial omission and resulted in termination of the trial and initiation of black-out period.

The time between the end of one response period and the beginning of the next response period was always 480 sec, inclusive of the time required for the delay and for food or drug delivery. The delay and the inter-trial interval ran simultaneously to ensure that reinforcement rate did not vary with delay. Each reinforcer delivery or trial omission initiated an inter-trial blackout period during which lights were extinguished and levers were retracted. The duration of the inter-trial blackout varied as a function of the delay to delivery of the preceding reinforcer.

Effects of different doses of remifentanyl and/or delays to either food or drug delivery were examined. A delay/dose combination remained in effect within and across sessions until the total number of reinforcers received and number of infusions received did not vary by more than ± 2 across 3 consecutive sessions. Conditions were studied in an irregular order within and across monkeys. Prior to determining the dose-effect curve, the reinforcer associated with each lever (food or an infusion of 0.32 $\mu\text{g/kg}$ of remifentanyl) was switched at least twice for each monkey. Thereafter, the reinforcers associated with each lever were fixed for a particular monkey for the remainder of the experiment. Remifentanyl dose-effect curves were determined by varying the dose available when both food and drug were delivered immediately. Initially, monkeys chose between food and 0.32 $\mu\text{g/kg}$ /infusion of remifentanyl. Once responding was stable, saline or smaller doses of remifentanyl were studied. Tests with each dose were followed by sessions in which monkeys chose between 0.32 $\mu\text{g/kg}$ /infusion of remifentanyl and food, after which another dose (or saline) was substituted for 0.32 $\mu\text{g/kg}$ /infusion of remifentanyl. The dose of remifentanyl was decreased in half-log unit increments until monkeys chose drug no more than twice per session for 3 consecutive sessions (the maximum number of infusions received when saline was available). The smallest doses tested were 0.01 $\mu\text{g/kg}$ /infusion for monkey EL and 0.032 $\mu\text{g/kg}$ /infusion for monkeys ME and GA.

After dose-effect curves were established with food and drug delivered immediately, the effects of delaying drug delivery were assessed beginning with the smallest dose of remifentanyl that maintained at least 80% responding for drug in all monkeys (0.32 $\mu\text{g/kg}$ /infusion). Initially, monkeys chose between immediate delivery of 0.32 $\mu\text{g/kg}$ /infusion and immediately delivery of food. The delay (30-240 sec) to drug delivery varied until a delay curve was obtained that ranged from a delay that did not reduce responding for drug (i.e., at least 80% of reinforcers were infusions) to a delay that reduced responding for drug to less

than 20%. Different delay conditions were always separated by a no-delay condition; when responding under one delay was stable, the delay was removed for at least 3 sessions (and until responding was stable), then another delay was introduced. If a delay did not reduce responding for drug to less than 80%, saline was substituted for drug to confirm that the monkey would respond for food. Once the monkey reliably responded for food when the choice was between food and saline, 0.32 $\mu\text{g/kg}$ /infusion of remifentanyl was delivered immediately, followed by determination of another delay. Delayed delivery of a larger dose of remifentanyl (1.0 $\mu\text{g/kg}$ /infusion) was studied in the same manner.

Effects of delaying food delivery when the alternative was immediate delivery of remifentanyl were determined in a similar fashion. Either saline or a dose of remifentanyl that did not maintain greater than 20% responding for drug was available with both reinforcers available immediately. After responding stabilized, a delay (60-240 sec) was added to the delivery of food while infusions continued to be delivered immediately. The effects of different delays were tested across conditions which were separated by a no-delay condition. If a delay did not increase responding for drug to greater than what was obtained with no delay, then 0.32 $\mu\text{g/kg}$ /infusion of remifentanyl was made available to confirm that the monkey would respond for drug. Once the monkey reliably responded for drug, either saline or the smaller dose of remifentanyl was available immediately and the effects of another delay were determined. At least 2 doses of remifentanyl and saline were studied with delayed food for each monkey.

Remifentanyl hydrochloride (Bioniche Pharma, Lake Forest, IL, USA) was dissolved in 0.9% saline (0.15-15.0 $\mu\text{g/ml}$). Infusion durations ranged from 9 to 17 sec. Saline infusion durations were matched to the duration used during the immediately preceding condition with remifentanyl.

Data analysis

The number of trials completed, the number of food and drug reinforcers received, and the percentage of drug reinforcers received was obtained for each session. The means ($\pm$ range) of the last 3 sessions were calculated for each condition and plotted as a function of unit dose of remifentanyl (when both alternatives were delivered immediately) or as a function of delay when either food or drug was delayed. Overall response rates were calculated by dividing the sum of left and right lever responses during choice trials by the total time spent in response periods. The dose of drug estimated to produce 50% drug choice (i.e., ED_{50}) was interpolated using data comprising the ascending limb of dose-effect curves obtained when both reinforcers were delivered immediately, when drug delivery was delayed, and when food delivery was delayed. This portion of the function included data ranging from the largest dose that maintained no more than 20% responding for drug to the smallest dose that maintained at least 80% responding for drug.

Results

Across all conditions, monkeys required on average of 4.5 (median = 4; range = 3 to 12) sessions to satisfy the stability criteria; the number of sessions did not appear to vary systematically across conditions or monkeys. When monkeys could choose between immediate delivery of food or saline, they responded predominantly for food (Figure 1, data above "S"), receiving fewer than 2 infusions (filled circles) and at least 8 food pellets (open circles). Small doses of remifentanyl did not maintain responding for drug greater than that maintained by saline. Increasing the dose of remifentanyl to 0.1 (EL) and 0.32 (ME and GA) $\mu\text{g/kg}$ /infusion increased responding for drug and resulted in greater than 8 infusions and fewer than 2 food pellets. This level of responding was maintained in all monkeys when a larger dose (1.0 $\mu\text{g/kg}$ /infusion) of remifentanyl was available.

With increasing delays to the delivery of 0.32 $\mu\text{g/kg}$ /infusion (circles, Figure 2), the percentage of infusions received decreased indicating that responding for drug decreased and responding for food increased. Delaying drug delivery by 120 (EL and ME) or 240 (GA) sec decreased responding for drug to less than 20% (and to greater than 80% for food). For all monkeys, delaying delivery of the larger dose of remifentanyl (1.0 $\mu\text{g/kg}$ /infusion; squares, Figure 2), up to the longest delay tested (240 sec), had no effect on the percentage of responding for drug.

The effects of delaying the delivery of food, shown in Figure 3, depended upon the dose of remifentanyl. For monkey EL (left panel), 0.032 $\mu\text{g/kg}$ /infusion remifentanyl (inverted triangles) maintained 23% responding for drug when drug and food were delivered immediately. Delaying food delivery by 120 sec increased responding for drug. Likewise, for monkeys ME and GA, 0.1 $\mu\text{g/kg}$ /infusion (diamonds, center and right panels, Figure 3) maintained less than 20% responding for drug when food and drug were delivered immediately. Delaying food delivery by 60 (ME) or 120 (GA) sec increased responding for drug.

When a smaller dose of remifentanyl was available, increasing the delay to food increased responding for drug and decreased responding for food in monkey EL; however, the delay curve for this monkey was shifted rightward as compared to the delay curve obtained with the larger dose (left panel, Figure 3). Likewise, in monkey GA, delaying the delivery of food increased responding for a smaller dose of remifentanyl with the delay curve shifted rightward as compared to the delay curve obtained with a larger dose (compare diamonds and inverted triangles, right panel, Figure 3). However, in monkey ME, 0.032 $\mu\text{g/kg}$ /infusion (center panel, Figure 3) failed to maintain responding for drug up to a 240-sec delay to the delivery of food. That is, in this monkey delaying food delivery had no effect across the range of delays tested when the smaller dose was available for immediate delivery. Delaying food delivery when saline was available immediately (circles) increased responding for saline to a maximum of 18, 27, and 27% in monkeys EL, ME, and GA, respectively (Figure 3).

Response rates decreased by up to 80% when infusions or food were delayed 120-240 sec (Table 1). Reductions in rate, however, were generally not associated with reductions in the total number of reinforcers delivered as monkeys received at least 9 total reinforcers. In one exception, monkey EL received an average of 7.3 reinforcers per session when the choice was between immediate delivery of saline and delivery of food delayed by 240 sec. Across all conditions and monkeys the average total number of responses emitted per reinforcer was 5.1 (range: 5.0 to 5.6) which did not vary with dose of remifentanyl or delay, indicating that monkeys responded predominantly on one lever in each trial.

Figure 4 shows remifentanyl dose-effect curves with no delays (circles), delay to the delivery of food (upright triangles), and delay to delivery of drug (inverted triangles for EL and ME; diamonds for GA). Delaying the delivery of drug by 120 (EL and ME) or 240 (GA) sec shifted the remifentanyl dose-effect curve rightward whereas delaying the delivery of food by 120 sec shifted the dose-effect curve leftward.

Discussion

In the current study, rhesus monkeys responded on one lever to receive one 300-mg food pellet and on another lever to receive an i.v. infusion. With increasing doses of remifentanyl, monkeys increasingly chose drug over food, replicating previous studies with other mu opioid receptor agonists such as heroin (e.g., Negus 2005) and with commonly abused drugs such as cocaine (e.g., Nader and Woolverton 1992; Paronis et al. 2002; Negus 2003).

Similar dose-effect relationships have been reported in humans choosing between cocaine and non-drug reinforcers such as money or vouchers exchangeable for food or other goods (e.g., Stoops et al. 2012). The current study examined the impact of dose of remifentanyl on delay discounting of food and of remifentanyl in rhesus monkeys. To date only a limited range of conditions has been examined using drug versus food choice procedures. While previously published studies have systematically varied delay to delivery of drug, the effects of systematically varying delay to delivery of a non-drug reinforcer, using a drug versus food choice procedure, have not been studied as extensively. In the current study, delaying the delivery of either food or drug altered choice in a manner consistent with the view that imposing a delay between a response and the delivery of its consequence reduces preference for that consequence and enhances preference for an alternative.

Imposing a delay to the delivery of a dose of drug (0.32 $\mu\text{g/kg/infusion}$) that otherwise maintained exclusive responding, decreased responding for drug and increased responding for food, shifting the remifentanyl dose-effect curve rightward, indicating that delaying drug reduces the potency of remifentanyl to serve as a positive reinforcer. Previous reports with rhesus monkeys have shown that delays can also decrease responding for cocaine under a single-response self-administration procedure (Beardsley and Balster 1993). Moreover, delaying cocaine delivery reduces responding for cocaine under a choice procedure when the alternative is immediate delivery of food (Woolverton and Anderson 2006) or immediate delivery of a smaller dose (Woolverton et al. 2007). The effects of delaying drug delivery are functionally similar to other manipulations presumed to reduce drug choice. For example, increasing the fixed-ratio requirement to obtain an infusion of cocaine also reduces drug choice and shifts the cocaine dose-effect curve rightward (Nader and Woolverton 1992; Negus 2003; Czoty et al. 2005; Banks et al. 2012). Taken together, these results indicate that drug taking (i.e., potency as a positive reinforcer) is significantly altered by factors related to drug delivery such as delaying delivery or increasing cost.

Delaying the delivery of food shifted the remifentanyl dose-effect curve leftward in a manner consistent with the view that delaying food delivery increased the potency of remifentanyl to serve as a positive reinforcer. For all three monkeys, a dose was identified (0.032 for EL, and 0.1 $\mu\text{g/kg/infusion}$ for ME and GA) that did not reliably maintain responding for drug when both food and drug were delivered immediately. Delaying food delivery increased responding for that otherwise non-preferred dose of drug, shifting the remifentanyl dose-effect curve to the left. These data suggest that a switch from responding predominantly for food to responding predominantly for drug, as the delay to the delivery of food increased, was not simply avoidance of delayed reinforcers; otherwise, monkeys would be expected to respond for the immediate alternative, regardless of its magnitude. Rather, the effects of delaying the delivery of food were modulated by the dose of remifentanyl available as the immediate alternative. When the dose of drug was reduced, longer delays to the delivery of food were required to increase responding for drug (EL and GA). For one monkey (ME), responding for drug was not substantially increased up to the longest delay tested. Likewise, when the alternative was saline, delaying food had little effect on responding for infusions. These results are similar to those reported by Woolverton and Anderson (2006) in that delaying delivery of food increased responding for the alternative drug reinforcer. In their study, the alternative was delayed delivery of a dose of cocaine that otherwise (i.e., when food and drug were delivered immediately) maintained high levels of responding.

The effects of delaying the delivery of food in the current study are consistent with effects reported in humans given a choice between drug and non-drug reinforcers. For example, in one study (Vuchinich et al. 1987) undergraduate students could choose between an alcoholic drink delivered immediately and the opportunity to win money that would be delivered immediately or after a delay of up to 8 weeks. Responding for alcohol was inversely related

to the amount of money (i.e., subjects responded less for alcohol when larger sums of money could be won) and directly related to the delay to receipt of the money. That is, subjects responded more for alcohol when receipt of money was delayed. This effect has been demonstrated more recently in smokers who could choose between puffs of a cigarette available immediately and money available immediately or after a delay of up to 3 weeks (Roll et al. 2000). As in the current study, drug choice was enhanced when the receipt of an alternative, non-drug reinforcer was delayed.

When either food or drug was delayed, response rates were decreased by as much as 50 to 80% (of control rates) for some monkeys; however, monkeys continued to receive 9 to 10 total reinforcers per trial, and under some conditions rate-decreasing effects occurred in the absence of any change in preference, demonstrating that delays can impact multiple dimensions of behavior independently. While delaying reinforcement can change the allocation of behavior from one alternative to another (e.g., Chung and Herrnstein 1967) and can also decrease rates of responding (e.g., Sizemore and Lattal 1978), changes in preference and rate do not always covary. In the current study when food was delayed and the alternative was an immediate infusion of saline, monkeys continued to respond for food, but did so at reduced rates of responding. These results indicate that delay to reinforcement can impact rates of responding for a delayed reinforcer; however, changes in preference appear to depend upon other factors such as the magnitude of the immediately available alternative.

In summary, this study demonstrates that the mu opioid receptor agonist remifentanyl dose dependently increases responding for drug and decreases responding for food in rhesus monkeys responding under a food-versus-drug choice procedure and provides evidence that drug choice is sensitive to delayed delivery of drug and to delayed delivery of food. When given a choice between food and drug, delaying the delivery of a drug decreases its potency to serve as a positive reinforcer; perhaps more importantly, delaying the delivery of a non-drug reinforcer (i.e., food) increases the potency of a drug to serve as a positive reinforcer. These results underscore the importance of environmental context in which drugs and other reinforcers are available and they suggest that understanding the factors that control substance (e.g., opioid) abuse requires examination of contingencies for both drug and non-drug reinforcers.

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Figure 1.

The number of reinforcers (infusions, closed circles; food pellets, open circles) received, when both reinforcers were available immediately, plotted as a function of dose of remifentanyl (μg/kg/infusion) for individual monkeys. Each data point represents the mean (± range) from the last 3 sessions under each condition. “S” = saline.

Figure 2.

The percentage choice for drug (number of infusions divided by total reinforcers received * 100) plotted as a function of delay (sec) to the delivery of 0.32 (circles) or 1.0 (squares) µg/kg/infusion of remifentanyl. Each data point represents the mean ($\pm$ range) from the last 3 sessions under each condition.

Figure 3.

The percentage choice for drug or saline plotted as a function of delay (sec) to food delivery when the immediately available alternative was saline (circles), 0.01 (upright triangles), 0.032 (inverted triangles), or 0.1 (diamonds) $\mu\text{g/kg/infusion}$ of remifentanyl. See Figure 2 for other details.

Figure 4.

The percentage choice for drug plotted as a function of dose of remifentanyl when both reinforcers were available immediately (circles), when food was delayed by 120 sec (upright triangles), and when drug was delayed either 120 sec (inverted triangles; monkeys EL and ME) or 240 sec (diamonds; monkey GA). See Figure 2 for other details.

Table 1Mean ($\pm$ SEM) response rate (responses/sec) under each experimental condition

Monkey	Dose of remifentanyl (μg/kg/infusion)	No delay	Delay (sec) to drug				Delay (sec) to food			
			30	60	120	240	60	120	240	
EL	Saline	0.61 (0.18)						0.40 (0.02)	0.27 (0.06)	
	0.01	0.36 (0.06)						0.58 (0.09)	0.45 (0.07)	
	0.032	0.43 (0.04)					0.43 (0.04)	0.78 (0.11)		
	0.1	1.08 (0.18)								
	0.32	0.96 (0.08)	0.75 (0.17)	0.78 (0.13)	0.41 (0.12)					
ME	1.0	2.75 (0.02)		0.48 (0.14)	0.57 (0.15)					
	Saline	2.87 (0.05)						3.13 (0.22)	2.47 (0.2)	
	0.032	3.49 (0.19)						2.90 (0.29)	2.29 (0.13)	
	0.1	4.38 (0.14)					4.09 (0.92)	3.03 (0.63)		
	0.32	4.85 (0.39)		3.25 (0.74)	2.56 (0.12)	2.32 (0.06)				
GA	1.0	7.20 (0.17)				2.99 (0.18)				
	Saline	2.07 (0.12)						1.33 (0.17)	0.72 (0.06)	
	0.032	1.38 (0.11)						1.87 (0.14)	1.03 (0.11)	
	0.1	2.05 (0.04)						2.45 (0.09)		
	0.32	1.71 (0.02)	1.10 (0.19)	1.53 (0.13)	1.66 (0.06)					
	1.0	3.34 (0.08)				3.17 (0.03)				