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Delay discounting of the mu opioid receptor agonist remifentanyl in rhesus monkeys

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Abstract

Although increased impulsivity (delay discounting) is an important risk factor for drug abuse, the impact of delay on drug taking has received relatively little attention.

This study examined delay discounting of the mu opioid receptor agonist remifentanyl in rhesus monkeys (n=4) responding for intravenous (i.v.) infusions under a concurrent choice procedure. Dose-effect curves for remifentanyl were determined by varying the dose available on one lever (0.001-0.32 µg/kg/infusion) while keeping the dose available on the other lever (0.1 µg/kg/infusion) the same. Dose-effect curves were determined when both infusions were delivered immediately and when delivery of the fixed dose was delayed (15-180 s).

When both doses of remifentanyl were delivered immediately, monkeys chose the large dose. Delaying delivery of the fixed dose reduced choice of that dose and increased choice of small immediately available doses.

Extending previous studies these results show that the effects of delay on choice between two doses of a mu opioid receptor agonist are consistent with hyperbolic discounting. Delaying delivery of a preferred reinforcer (e.g., large dose of drug) reduces its effectiveness and increases the effectiveness of small immediately available doses. This effect of delay, particularly on drug self-administration, might contribute to drug abuse.

Keywords

delay discounting; drug self-administration; drug abuse; opioid receptor agonist; rhesus monkey; remifentanyl

Introduction

Delay discounting is a process through which the effectiveness (e.g., subjective value) of a reinforcer decreases as the delay to its presentation increases (e.g., Rachlin et al., 1991;

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Green and Myerson, 2004). The relationship between the value of a reinforcer and delay is described by a hyperbolic discounting function (Mazur, 1987):

$$V=A/(1+kD) \quad (\text{Equation 1})$$

where V is the value of the delayed reinforcer, A is the amount (or undiscounted value) of the delayed reinforcer, k is a free parameter that indicates the rate of discounting, and D is the time between a response and presentation of the reinforcer. Delay discounting is thought to be important to behavior that reflects greater impulsivity (e.g., Rachlin and Green, 1972; Ainslie, 1975; Logue, 1988; Madden and Bickel, 2010) and has become increasingly important for understanding certain behavior including drug abuse. Enhanced discounting might predispose an individual to choose the more immediate effects of using drug rather than the delayed benefits of remaining abstinent such as health, income, and positive social interactions. Indeed, drug abusers tend to discount the value of delayed rewards (e.g., money or drugs) more rapidly than non-users (e.g., Bickel and Marsh, 2001; Reynolds, 2006; Yi et al., 2010; MacKillop et al., 2011). Moreover, enhanced discounting has been linked to a variety of risky behaviors associated with drug abuse, such as having unprotected sex and sharing needles (e.g., Odum et al., 2000; Herrmann et al., 2014) and is predictive of poorer treatment outcomes (e.g., Moeller et al., 2001).

Although enhanced discounting is thought to be an important risk factor for drug abuse (e.g., Bickel et al., 2012, 2014), the impact of delay on drug taking has received relatively little attention. The majority of data on discounting of drug reinforcers comes from studies with humans making choices between different hypothetical amounts of drug (e.g., Madden et al., 1997). Understanding how delay impacts drug taking and how the impact of delay varies across different histories (e.g., after chronic drug use) will facilitate a better understanding of the basic processes underlying drug abuse and will aid in developing more effective prevention and treatment strategies.

Recent studies in nonhuman primates indicate that delay substantially impacts drug-reinforced behavior. For example, Woolverton and colleagues showed that delay impacts self-administration of cocaine in monkeys working under choice procedures. When given a choice between a small dose of cocaine delivered immediately and a large dose of cocaine delivered after a delay, responding for small doses of cocaine increased with longer delays to delivery of the large dose (Woolverton and Anderson, 2006; Woolverton et al., 2007). Importantly, Woolverton et al. (2007) demonstrated that decreased responding for delayed cocaine, and increased responding for immediate cocaine, was described well by a hyperbolic discounting function similar to Equation 1 (Mazur, 1987). Despite quantitative differences in behavior (e.g., rate of discounting), the hyperbolic nature of discounting of cocaine is similar to discounting of saccharin in rhesus monkeys (Freeman et al., 2009), grain in pigeons (Mazur, 1987), water in rats (Richards et al., 1997), as well as a variety of real and hypothetical reinforcers in humans (e.g., Johnson and Bickel, 2002), providing compelling evidence for the generality of the delay discounting process (function) across species and reinforcers.

Given the significant and growing misuse and abuse of opioids (e.g., Manchikanti et al., 2012) and the fact that discounting appears to be a critical factor in opioid abuse (e.g., Madden et al., 1997; Kirby et al., 1999; Giordano et al., 2002), recent studies have extended the generality of these findings to self-administration of a mu opioid receptor agonist. Consistent with earlier studies using cocaine (e.g., Anderson and Woolverton, 2006; Woolverton et al., 2007), delaying delivery of a large dose of the mu opioid receptor agonist remifentanyl increases choice of small immediately available doses of remifentanyl in rhesus monkeys (Maguire et al., 2013a). While that previous study extended the generality of the findings by Woolverton and colleagues to another drug class (mu opioid receptor agonists), the rate at which remifentanyl is discounted has not been assessed.

The current experiment extends prior studies by assessing delay discounting of remifentanyl in rhesus monkeys responding under a concurrent choice procedure. Monkeys could choose between two doses of remifentanyl with the delay to delivery of one (large) dose systematically varied in order to generate delay functions. The current study used a procedure whereby dose-effect curves for remifentanyl were determined more rapidly (i.e., one dose studied per day) than previous studies. In so doing, one goal of this study was to establish an experimental framework suitable for studying the impact of other factors (e.g., drug dependence) on the relationship between delay discounting and drug taking. Like other mu opioid receptor agonists (e.g., heroin), remifentanyl is readily self-administered by nonhuman subjects (e.g., Ko et al., 2002) and has positive reinforcing effects comparable to heroin (e.g., Panlilio and Schindler, 2000). The faster onset and shorter duration of action of remifentanyl, compared with heroin, are preferable under experimental conditions in which subjects make repeated choices because drug accumulation is limited or avoided.

Methods

Subjects

Four adult rhesus monkeys (*Macaca mulatta*), 2 females (SO and OL) and 2 males (GI and MO), were used in this study; SO and MO participated in a previous study (Maguire et al., 2013a). Body weight (6-10 kg) was maintained by post-session feeding (Harlan Teklad, High Protein Monkey Diet, Madison, WI, USA). Monkeys received fresh fruit and peanuts daily and water was continuously available in home cages. Subjects were housed individually under a 14/10-h light/dark cycle with lights on at 06.00 h; experimental sessions started at 13.00 h and lasted approximately 100 min. 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

Subjects were seated in commercially available chairs (Model R001; Primate Products, Miami, FL) and positioned in ventilated, sound-attenuating operant conditioning chambers. Each chamber contained a custom-made response panel with 2 horizontally aligned, retractable levers (Model ENV-612M, Med Associates, Inc., St. Albans, VT) located below

3 horizontally aligned lights; the two side lights could be illuminated green and the center light could be illuminated white. Infusions of drug or saline were delivered i.v. through a double-lumen catheter (Model SIL-C50-HSC1, Instech Solomon, San Antonio, TX); each lumen was connected to a subcutaneous (s.c.) access port (Model MID-C50; Access Technologies, Skokie, IL). Each port was connected through a 20-g Huber-point needle (Access Technologies) and a 183-cm mini-volume catheter extension set (Model 2C5687, Baxter Healthcare, Deerfield, IL) to a 30-ml syringe mounted in a syringe driver (Model PHM-100, Med Associates) that infused solution at a rate of 2.3 ml/min. A Med Associates interface and a PC-compatible computer controlled experimental events and recorded data. White noise was presented in the chamber to mask extraneous sounds, and an exhaust fan provided ventilation.

Surgery

Catheters were surgically implanted as described previously (Maguire et al. 2103a). Briefly, 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). The double-lumen catheter was implanted in a vein (e.g., jugular or femoral) and tunneled s.c. to the midscapular region of the back; each lumen was then connected to an access port.

Behavioral procedure

Monkeys were trained to lever-press for i.v. infusions of remifentanyl as described previously (Maguire et al., 2013a). Daily sessions were divided into 3 blocks, each comprising 2 forced trials followed by 6 choice trials. At the beginning of a block (i.e., the first forced trial), one side green light was illuminated and the lever located directly beneath that light was extended. Thirty responses immediately retracted the lever, turned off the green light, and illuminated the white center light. When an infusion was delivered immediately, the white light flashed on for 0.2 s and was then turned off. When the infusion was delivered after a delay, the white light was illuminated continuously for the duration of the delay and then turned off. In both cases, turning off the white light initiated the infusion and started an inter-trial blackout period during which all lights were off and the levers remained retracted. The infusion duration varied depending on body weight and the unit dose of remifentanyl (see “Drugs”). The duration of the blackout period was adjusted each trial such that the time between completion of one response period, signaled by retraction of the lever(s) and extinguishing of the green light(s), and initiation of the next response period was held constant at 200 s. During the second trial of each block (i.e., the second forced trial), the other green light was illuminated and its corresponding lever was extended; 30 responses delivered an infusion of saline or remifentanyl either immediately or after a delay as described above. The order of forced trials (right/left or left/right) remained the same across blocks within a session but varied quasi-randomly across sessions with the constraint that the same order was not presented for more than two consecutive sessions.

During choice trials, both green side lights were illuminated and both levers were extended. The contingencies associated with responding on either lever during choice trials were identical to those presented during the forced trials. In addition, responding on one lever

reset the ratio requirement on the other lever; thus, 30 consecutive responses on one lever were required to complete a choice trial. Both forced trials had to be completed in order to initiate choice trials within a block. Each block lasted 33 min; blocks were separated by a 60-s timeout period, during which the levers were retracted and all lights were off. The contingencies for each block within a session were identical.

Experimental design

Initially, responding on one lever delivered 0.32 $\mu\text{g/kg}$ /infusion of remifentanyl immediately and responding on the other lever delivered saline immediately; the side delivering remifentanyl was randomly determined across monkeys. After one session with at least 75% choice of remifentanyl across all choice trials of the session (see Data Analyses), the lever designations were switched for the next session and until choice of remifentanyl was at least 75% for the session. The experiment began following two such alternations.

Immediate delivery of the fixed dose

Remifentanyl dose-effect curves were determined for responding on one lever (variable-dose lever; A) when a constant (fixed) dose of remifentanyl was available on the other lever (fixed-dose lever; B). Monkeys initially chose between 0.32 $\mu\text{g/kg}$ /infusion of remifentanyl on lever A and 0.1 $\mu\text{g/kg}$ /infusion of remifentanyl on lever B, both delivered immediately. After one session with at least 75% choice of the large dose (lever A), the unit dose available on that lever decreased each session in half-log unit increments (from 0.32 $\mu\text{g/kg}$ /infusion) until percent choice of the variable dose was less than 25%. Thereafter, the dose available on lever A increased to 0.32 $\mu\text{g/kg}$ /infusion with the dose available on lever B remaining unchanged at 0.1 $\mu\text{g/kg}$ /infusion. The remifentanyl dose-effect curve without delay was determined multiple times before tests with delays were conducted.

Delayed delivery of the fixed dose

Once the remifentanyl dose-effect curve was established, effects of delay were assessed. Initially, monkeys chose between 0.32 $\mu\text{g/kg}$ /infusion of remifentanyl on lever A and 0.1 $\mu\text{g/kg}$ /infusion of remifentanyl on lever B, both delivered immediately. After one session with at least 75% choice of the large dose (lever A), delivery of the fixed dose (lever B) was delayed by 15, 30, 60, 120, or 180 s, with monkeys choosing between 0.32 $\mu\text{g/kg}$ /infusion delivered immediately and 0.1 $\mu\text{g/kg}$ /infusion delivered after a delay. Then, the dose available on lever A decreased each session (as described above), with the dose and delay on lever B remaining constant across sessions until one of three possible outcomes occurred: 1) percent choice for the variable dose was less than 25%; 2) the dose was decreased to 0.001 $\mu\text{g/kg}$ /infusion; or 3) fewer than 9 choice trials were completed for an entire session. Thereafter, the dose available on lever A increased to 0.32 $\mu\text{g/kg}$ /infusion with the dose available on lever B remaining unchanged at 0.1 $\mu\text{g/kg}$ /infusion delivered immediately. Tests with different delays were separated by dose-effect curve determinations without delay. Each delay condition was tested once per monkey, and the order with which different delays were tested varied across monkeys.

Occasionally, saline was substituted for remifentanyl on lever A and monkeys could choose between saline and 0.1 $\mu\text{g/kg}$ /infusion of remifentanyl, both delivered immediately. Saline

remained available for responding on lever A until percent choice of that lever (i.e., choice of the saline lever) was less than 25% for a session.

Drugs

Remifentanyl hydrochloride (Bioniche Pharma, Lake Forest, IL) was dissolved in 0.9% sterile saline and delivered i.v. Infusion durations were calculated each session based on body weight, the unit dose of remifentanyl, and the infusion rate; infusion duration ranged from 3 to 17 s. When one of the alternatives was saline, the infusion duration was matched to the infusion duration associated with the concurrently alternative dose of remifentanyl. In order to maintain patency, catheters were flushed and locked after each session with 2.5 ml of heparinized saline (100 Units/ml; Hospira, Inc., Lake Forest, IL).

Data Analyses

Percent choice of the variable dose of remifentanyl was calculated for each session by dividing the number of ratios completed on lever A during choice trials by the total number of ratios completed on levers A and B during choice trials and multiplying by 100. Percent choice was then plotted as a function of the variable dose for each delay condition. Dose-effect curves determined contemporaneous with each delay test were used as control dose-effect curves for individual subjects.

Effects of delay on choice were quantified by calculating the area above the dose-effect curve for the immediate infusion of remifentanyl (lever A). In order to calculate area, both axes were scaled using arithmetic units; the vertical axis ranged from 0 to 100; the horizontal axis ranged from 1 at the smallest dose (0.001 $\mu\text{g/kg/infusion}$) of remifentanyl tested to 6 at the largest dose of remifentanyl tested (0.32 $\mu\text{g/kg/infusion}$), resulting in a possible area ranging from 0 to 500. This area was taken as an index of the relative value of the variable dose versus the fixed dose under each delay condition. Decreases in area above the curve reflect increased choice of the variable (immediate) dose and decreases in choice of the fixed (delayed) dose. For individual monkeys, area was plotted as a function of delay to the fixed dose. Data were fitted using non-linear regression with Equation 1 (see "Introduction"), where V indicates area above the dose-effect curve for the variable dose (i.e., its value when the fixed-dose is delayed), A indicates area above the dose-effect curve for the variable dose in the absence of delay (i.e., the value of the variable dose when the fixed dose is immediate), k indicates rate of discounting, and D is the delay in seconds to delivery of the fixed dose of remifentanyl. GraphPad Prism (version 5.04, La Jolla, CA) was used to calculate area above the dose-effect curve and to fit delay functions.

Results

When given a choice between 0.32 $\mu\text{g/kg/infusion}$ on one lever (A) and 0.1 $\mu\text{g/kg/infusion}$ on the other lever (B), both delivered immediately, monkeys chose the large dose of remifentanyl exclusively (Figure 1A, data above 0.32). Choice of the variable dose decreased as the dose on the variable lever decreased (filled circles). When the same dose of remifentanyl (0.1 $\mu\text{g/kg/infusion}$; vertical dashed line) was delivered immediately on both levers, monkeys chose each option almost equally often with a slight bias in favor of the

fixed dose lever (57% of choice trials). When the variable dose decreased to 0.032 $\mu\text{g/kg}$ /infusion, choice for the variable dose decreased to 13%, and when the dose on the variable lever decreased further (0.01 $\mu\text{g/kg}$ /infusion) or when saline was substituted for remifentanyl on the variable dose lever, monkeys chose the fixed dose of 0.1 $\mu\text{g/kg}$ /infusion on lever B exclusively (data not shown). When both infusions were delivered immediately, monkeys completed all of the choice trials each session (18 total).

Delaying delivery of the fixed dose of remifentanyl on one lever (B) increased choice of small immediately delivered infusions of remifentanyl on the other lever (A) in a delay-dependent manner (Figure 1A, open symbols). Delays of 15 or 30 s did not substantially impact choice (squares and upright triangles, respectively) and, with the exception of monkey GI, did not impact the number of choice trials completed per session (Table 1). Increasing the delay to 60 s shifted the variable dose-effect curve leftward (inverted triangles), increasing choice of an immediate infusion of 0.1 $\mu\text{g/kg}$ /infusion on lever A from 43% without delay to 65%, choice of 0.032 $\mu\text{g/kg}$ /infusion from 13 to 63%, and choice of 0.01 $\mu\text{g/kg}$ /infusion from 0 to 41%. Of the 3 monkeys tested with 0.0032 $\mu\text{g/kg}$ /infusion, choice of this dose remained low (9.7%), and for one monkey (GI), the number of trials completed was decreased by half (Table 1). Delaying the fixed dose by 120 or 180 s (circles and diamonds, respectively) further increased choice of small doses (0.01 $\mu\text{g/kg}$ /infusion) of remifentanyl to between 40 and 60%. The effect of 120 and 180-s delays on choice did not differ substantially; however, a 180-s delay markedly decreased the number of choice trials completed in 3 of 4 monkeys, compared with the 120-s delay condition which decreased the number of choices in only 1 monkey (Table 1).

Area above the dose-effect curve for the variable dose of remifentanyl decreased with increasing delays to the fixed dose (Figure 1B), reflecting a delay-dependent increase in choice of the immediate dose of remifentanyl. The hyperbolic function provided a better fit for some monkeys than others (Table 2); the median R^2 value was 0.63 (range: 0.48-0.90). Without delay, the estimate of A (reflecting the relative value of each reinforcer without delay) was similar across monkeys with a median of 406 (range: 372-478). The median k value was 0.008 (range: 0.004–0.008).

Discussion

Opioid abuse is a significant and growing public health problem (e.g., Manchikanti et al., 2012), and delay discounting might contribute to the initiation and/or the maintenance of misuse and abuse (e.g., Madden et al., 1997; Kirby et al., 1999; Giordano et al., 2002). Thus, understanding how delay impacts opioid self-administration could help to identify behavioral factors that contribute to opioid abuse. Recent studies indicate that delay can substantially impact self-administration of drugs, including the mu opioid receptor agonist remifentanyl (Maguire et al., 2013a), insofar as delaying delivery of a large dose of drug increases responding for small immediately available doses of drug. The current study extends those results by assessing the rate of delay discounting of remifentanyl in rhesus monkeys choosing between two doses of remifentanyl under a similar, but not identical, choice procedure.

Remifentanyl dose-effect curves were determined by varying the dose available on one lever (0.001-0.32 $\mu\text{g/kg/infusion}$) while holding constant the dose of remifentanyl available on a second lever (0.1 $\mu\text{g/kg/infusion}$). When both infusions were delivered immediately, monkeys chose the large dose of remifentanyl over the small dose and were nearly indifferent when the same dose was available on both levers. These results are consistent with previous studies using concurrent choice procedures in rhesus monkeys (e.g., Galuska et al., 2006; Koffarnus and Woods, 2008) and indicate that choice between different doses of remifentanyl was sensitive to reinforcer amount (i.e., unit dose). Moreover, similarity in dose-effect curves across monkeys reflects similar sensitivity to the reinforcing effects of remifentanyl.

Consistent with a previous study (Maguire et al., 2013a), delaying delivery of a dose of remifentanyl on one lever decreased choice of that dose and increased choice of a small immediately delivered dose on the other lever. In addition, the current study demonstrates that the effects of delay on choice between two doses of remifentanyl are described well by a hyperbolic discounting function (Equation 1). Notwithstanding several procedural differences between studies, the results of the current study are remarkably similar quantitatively to those reported by Woolverton et al. (2007). In particular, estimates of the rate of discounting (k) obtained for individual monkeys in the current study (median: 0.008, range: 0.004-0.008) are within the range of values reported by Woolverton et al. (2007) for monkeys responding for cocaine (median: 0.008, range: 0.002-0.078), suggesting a similarity in the rate of discounting of self-administered drugs with different mechanisms of action and pharmacological activity.

These results, along with a previous study (Maguire et al. 2013a), confirm that the impact of delay on drug choice in nonhuman subjects is generalizable to other classes of drugs (opioids) and is not specific to cocaine. This study also provides clear evidence for both between- (i.e., consistent results among subjects in this and a prior study [Maguire et al., 2013a]) and within- (consistent results between the two monkeys [MO and SO] that were studied in this and the prior study) subject replication of the effects of delay on delay discounting of a μ opioid receptor agonist. Moreover, the current findings with remifentanyl, taken together with studies using cocaine, support the hypothesis that in nonhuman primates drug reinforcers in general might be discounted less steeply than non-drug reinforcers such as sweetened solutions (see Freeman et al., 2009; 2012). A recent study reported that the rate at which food is discounted depends upon whether food or drug (cocaine) is available as the immediately delivered alternative (Huskinson et al., 2015), demonstrating that the types of commodities that are available, as either the immediate or the delayed option, also impact discounting. It is not known whether monkeys in the current study might discount other opioids (e.g., heroin), drugs with different pharmacological mechanisms (e.g., cocaine), or non-drug reinforcers (e.g., food) at different rates.

The effects of delay were assessed using one delayed dose of remifentanyl (0.1 $\mu\text{g/kg/infusion}$). It is unclear whether larger or smaller doses would be discounting at different rates. Based on studies in humans, it might be expected that the magnitude of the delayed reinforcer (in this study, unit dose) would impact rate of discounting insofar as small doses are discounted more steeply than large doses (magnitude effect; e.g., Green et al. 1997).

However, that possibility seems unlikely insofar as the magnitude effect has not been reported in nonhuman subjects (e.g., Richards et al., 1997; Green et al., 2004; Freeman et al., 2012).

One goal of this study was to establish a procedure allowing for rapid and reliable determination of the effects of delay under a drug-drug choice procedure. Rapid adjustment in dose allows for more efficient determination of dose-effect curves which could be advantageous for some experimental designs (e.g., chronic drug treatment and discontinuation of chronic drug treatment). Under baseline (no delay) conditions, dose-effect curves were determined relatively rapidly (e.g., in 3 to 4 days as compared to many days or weeks in other studies; Maguire et al., 2013a) and were reliable across multiple determinations. When delivery of the large dose of remifentanyl was delayed, choice increased for small immediately delivered doses of remifentanyl; however, the dose-effect curve for immediately delivered infusions was flatter and not as dose related, compared with previous studies (e.g., Maguire et al., 2013a). The flatter dose-effect curve in this case is likely related to this particular procedure in which the variable dose changed daily, possibly reflecting insufficient time for responding to transition to stability. Although this procedure allowed for rapid determination of baseline dose-effect curves and the effect of delay on choice was systematic and consistent across all subjects, additional refinement of this procedure is necessary in order to reliably generate doses-effect curves that are suitable for other types of analyses (e.g., see Woolverton et al. 2007). For example, changing doses less frequently (e.g., every 2 or 3 days rather than daily) might provide more time for behavior to stabilize. With further modification, this procedure will likely prove to be useful for studying other aspects of the relationship between delay discounting and drug taking.

These data add to a small but growing literature that has explored the impact of delay on drug taking in nonhumans. Studies to date indicate that delaying delivery of an otherwise preferred reinforcer, whether food (Maguire et al., 2013b; Woolverton and Anderson, 2006; Huskinson et al. 2015) or a dose of drug (Maguire et al., 2013a; Woolverton and Anderson, 2006; Woolverton et al., 2007), increases responding for a small and less preferred reinforcer (e.g., small dose of drug). Delaying presentation of preferred commodities increases the effectiveness of small immediately-available commodities. Increases in the reinforcing effects of small doses of drug in the context of delayed alternative reinforcers might play a role in vulnerability to abuse drugs, particularly for individuals that are more sensitive to reinforcer delay.

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Figure 1.

A: Percent choice of the variable dose infusion of remifentanil (Lever A) delivered immediately (i.e., no delay), plotted as a function of dose. The dose available on the other alternative (Lever B) was 0.1 $\mu\text{g/kg/infusion}$, delivered either immediately or after a delay. The horizontal axes indicate the doses available on each alternative. Filled circles show data when both doses were delivered immediately. Open symbols indicate data when monkeys chose between an immediately available dose of remifentanil available on one lever (A) and the fixed dose of remifentanil available on the other lever (B) that was delivered after a delay of 15, 30, 60, 120, or 180 s. The shaded region around the filled data points (no delay) and the error bars on the open data points (delay) indicate the standard error of the mean. Unless otherwise indicated, each data point represents the mean of 4 monkeys; numbers in parenthesis indicate the number of monkeys contributing to each data point (see text for more detail).

B: Delay discounting function. Area above the dose-effect curve for the variable dose of remifentanil was calculated for individual monkeys for each delay condition. Area is plotted as a function of delay to delivery of the fixed dose of remifentanil. The solid line shows the fit of a hyperbolic discounting function for the group data (see text for data from individual monkeys). Data points indicate the group mean; error bars indicate the standard error of the mean.

Table 1

Choice trials completed for individual monkeys for each delay and dose condition

Delay (sec) to the fixed dose ^a (Lever B)	Variable dose (µg/kg/infusion) (Lever A)	Monkey			
		GI	MO	OL	SO
15 sec	0.32	18 ^b	18	18	18
	0.1	18	18	18	18
	0.032	18	18	18	18
	0.01			18	
	0.0032			18	
	0.001				
30 sec	0.32	18	18	18	18
	0.1	17	18	18	18
	0.032	17			18
	0.01				18
	0.0032				18
	0.001				
60 sec	0.32	18	18	18	18
	0.1	17	18	18	18
	0.032	18	18	18	18
	0.01	17	18	18	18
	0.0032	9		18	18
	0.001				
120 sec	0.32	18	18	18	18
	0.1	18	18	18	18
	0.032	14	18	18	18
	0.01	14	18	18	18
	0.0032	14	18	18	
	0.001	10	17	18	
180 sec	0.32	18	18	18	18
	0.1	11	15	18	18
	0.032	15	11	17	18
	0.01	18	10	18	17
	0.0032	12	7	18	9
	0.001	8	6	18	

^aThe fixed dose was 0.1 µg/kg/infusion^bEach session comprised 18 total choice trials^cEmpty cells indicate a dose and delay condition that was not tested

Table 2

Delay discounting parameters, A and k , as well as a measure of goodness of fit for individual monkeys.

Curve fit statistic	Monkey			
	GI	MO	OL	SO
A	418	438	393	372
k	0.008	0.007	0.008	0.004
R^2	0.90	0.72	0.48	0.53