Effect of Delay on Self-Administration of Remifentanyl under a Drug Versus Drug Choice Procedure in Rhesus Monkeys

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ABSTRACT

Drug abuse can be conceptualized as excessive choice of drug over other reinforcers, and factors that affect drug taking can be examined experimentally using choice procedures. This study examined the impact of reinforcer delay on self-administration of the μ -opioid receptor agonist remifentanyl in rhesus monkeys ($n = 4$) lever pressing under a concurrent fixed-ratio 30 schedule. Responding on either lever delivered an intravenous infusion of either remifentanyl or saline. Dose-effect curves were first determined when responding on one lever delivered remifentanyl and responding on a second lever delivered saline. Monkeys then chose between two doses of remifentanyl, and delay to delivery of the large dose was varied systematically. Responding for remifentanyl (0.01–1.0 $\mu\text{g/kg/infusion}$) increased dose-dependently when the alternative was saline or a dose of

remifentanyl. Delaying delivery of the large dose of remifentanyl by 30, 60, 120, or 240 seconds increased responding for smaller, immediately available doses (0.01–0.1 $\mu\text{g/kg/infusion}$) and, in some cases, increased responding for doses of remifentanyl that did not maintain responding when the alternative was saline. These data demonstrate that delaying the delivery of an opioid receptor agonist can significantly affect its reinforcing effectiveness. The imposition of a delay reduces the effectiveness of large doses of drug to maintain responding and increases the effectiveness of immediately available commodities, including smaller doses of drug. Increased reinforcing effectiveness of smaller doses of drug in the context of other delayed reinforcers might contribute to the development and maintenance of opioid abuse.

Introduction

Drug abuse remains a significant public health problem, particularly among adolescents and young adults (Johnston et al., 2013). An understanding of variables that contribute to the development and maintenance of drug abuse will aid in the identification of risk factors and to development of more effective treatments. Drug abuse can be conceptualized as excessive choice of drug over other nondrug reinforcers (Heyman, 2009). Variables that impact choice can be examined experimentally in preclinical research using a variety of procedures (see reviews by Bergman and Paronis, 2006; Banks and Negus, 2012). For example, increasing the cost of drug or decreasing the cost of alternative nondrug reinforcers reduces drug taking in human (Stoops et al., 2012) and nonhuman primates (Nader and Woolverton, 1992; Negus, 2003). In addition to altering cost, changing other parameters of reinforcement can also significantly affect drug taking, such as increasing the time between a response and delivery of a reinforcer.

Delay can impact operant behavior by decreasing rates of responding (Sizemore and Lattal, 1978) and by changing allocation of behavior from delayed alternatives to immediately available alternatives (Chung and Herrnstein, 1967). Moreover, delay can significantly affect drug-maintained behavior. For example, imposing a delay between completion of the response requirement and delivery of an infusion of cocaine decreases response rates in rhesus monkeys lever pressing under a single-response self-administration procedure (Beardsley and Balster, 1993). More recently, researchers (Anderson and Woolverton, 2003; Woolverton and Anderson, 2006; Woolverton et al., 2007) showed that delay impacts self-administration of cocaine under concurrent choice procedures. For example, when given a choice between smaller doses of cocaine delivered immediately and a large dose of cocaine delivered after a delay, rhesus monkeys responded less for the large, delayed dose and more for the smaller, immediately available doses (Woolverton and Anderson, 2006; Woolverton et al., 2007). Woolverton et al. (2007) further demonstrated that decreased choice of the large, delayed dose of cocaine was well described by a hyperbolic discounting function in a manner comparable to other types of reinforcers (Mazur, 1987), suggesting that choice involving drug and nondrug reinforcers is likely under the control of similar behavioral processes.

Delay is thought to be an important factor in drug abuse; current drug abusers discount the value of delayed reinforcers

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ABBREVIATIONS: There are no abbreviations in this article.

more rapidly than individuals who have never used drugs or former users (reviewed by Bickel and Marsch, 2001; Perry and Carroll, 2008; de Wit and Mitchell, 2010). In particular, opioid-dependent individuals discount the value of delayed reinforcers, such as money or drugs, more rapidly than nonusers and discount the value of drugs more rapidly than money (Madden et al., 1997; Kirby et al., 1999). Moreover, opioid-dependent individuals discount the value of delayed reinforcers (money or drugs) more rapidly during acute periods of withdrawal from opioids as compared with periods of buprenorphine maintenance (Giordano et al., 2002). Enhanced discounting might predispose an individual to choose the more immediately available effects of drug taking rather than the delayed benefits of remaining abstinent, such as health, income, and positive social interactions. Individuals who are more sensitive to delay prior to using drugs might be more likely to experiment with drugs; drug use also might enhance discounting and, thus, increase the likelihood of continued drug use (Bickel et al., 2012, 2013).

Given the continuing public health challenge associated with opioid abuse, particularly prescription opioid abuse (Compton and Volkow, 2006; Manchikanti et al., 2010; Johnston et al., 2013) and the apparent relationship between delay discounting and various aspects of opioid abuse (Madden et al., 1997; Giordano et al., 2002), this study examined the impact of delaying delivery of a large dose of the short-acting μ -opioid receptor agonist remifentanyl on choice when the alternative is a smaller, immediately available dose of remifentanyl. This study builds upon previous work using cocaine-maintained responding (e.g., Woolverton et al., 2007) by examining effects of delay on responding maintained by a μ -opioid receptor agonist. Moreover, this study examines the impact of delaying remifentanyl administration in a drug-drug choice procedure under conditions similar to previous work using a drug-food choice procedure (Maguire et al., 2013), which allows for examination of generality of effects. Remifentanyl was used in this study because, similar to other μ -opioid receptor agonists (e.g., heroin), it is readily self-administered by nonhuman primates. However, the faster onset and shorter duration of action of remifentanyl, compared with heroin, are preferable under conditions in which subjects can make repeated choices (i.e., limiting drug accumulation). Remifentanyl dose-effect curves were determined first when drug was available on one lever and saline was available on the other lever. Monkeys then could choose between two doses of remifentanyl; the delay to delivery of a large dose of remifentanyl and the dose of the smaller, immediately available alternative were varied systematically.

Materials and Methods

Animals. Four experimentally naïve adult rhesus monkeys (*Macaca mulatta*), 1 female (SO) and 3 males (MI, MO, and SH), were used in this study. Body weight (6–10 kg) was maintained by postsession feeding (High Protein Monkey Diet; Harlan Teklad, Madison, WI). Monkeys received fresh fruit and peanuts daily, and 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. Subjects were seated in commercially available chairs (model R001; Primate Products, Miami, FL) and positioned in ventilated, sound-attenuating operant conditioning chambers. The custom-made response panel in each chamber contained two retractable levers (model ENV-612M; Med Associates, Inc., Georgia, VT) located below three horizontally aligned lights; the two side lights could be illuminated green and the center light could be illuminated white. Drug or saline was delivered intravenously through either lumen of a silicone double-lumen catheter (model SIL-C50-HSC1; Instech Solomon, San Antonio, TX), which was surgically implanted (see "Surgery"). Each lumen of the catheter was connected to a subcutaneous access port (model MID-C50; Access Technologies, Skokie, IL). At the beginning of the session, 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, which was mounted in a syringe driver (model PHM-100; Med Associates, Inc.) that infused at a rate of 2.3 ml/min. An interface (Med Associates, Inc.) and a PC-compatible computer controlled experimental events and recorded data. White noise was continuously presented in the chamber to mask extraneous sounds.

Surgery. Monkeys were anesthetized with 10 mg/kg 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. The catheter was implanted in a jugular or femoral vein and tunneled subcutaneously to the midscapular region of the back; each lumen was then connected to an access port.

Initial Training. Lever pressing was initially established during daily, 30-minute sessions in which both levers were extended and green lights were illuminated directly above each lever. One response on either lever extinguished the green lights, retracted both levers, immediately illuminated the center white light for 0.2 second, and delivered one 300-mg food pellet (Dustless Precision Pellets F0179; Bio-Serv, Frenchtown, NJ). The next opportunity to respond, signaled by extension of the levers and illumination of green lights, began 1 second after food delivery. After monkeys received 50 pellets per session for three consecutive sessions, training was temporarily suspended and catheters were implanted.

Following surgery, monkeys rested for 3 days before training began under the choice procedure. Thereafter, sessions were conducted once daily, 7 days per week. Initially, sessions comprised two forced trials followed by up to 28 choice trials. Sessions ended after 28 choice trials were completed or 100 minutes, whichever occurred first. During the first forced trial, only one lever was extended and only the green light located above that lever was illuminated. Five responses (fixed-ratio 5) immediately retracted the lever, extinguished the green light, illuminated the center white light for 0.2 second, and activated the infusion pump, delivering the infusion of remifentanyl (or saline) associated with responding on that lever for that session. Completion of a trial initiated an intertrial interval, during which the levers remained retracted and all lights were extinguished, followed by initiation of the next trial; the intertrial interval was 180 seconds for all trials. During the second forced trial, the other lever was extended and the green light located directly above that lever was illuminated. Five responses immediately retracted the lever, extinguished the green light, illuminated the center white light for 0.2 second, and delivered the infusion associated with responding on that lever for that session. The order of forced trials (left/right or right/left) varied quasi-randomly from session to session with the constraint that the same order was not presented for more than two consecutive sessions. Both forced trials had to be completed to begin the choice-trial portion of the session.

The beginning of a choice trial was signaled by extension of both levers and illumination of both green lights. Five consecutive responses on either lever immediately retracted both levers, extinguished

both green lights, illuminated the center white light for 0.2 second, and delivered the infusion associated with that lever. Responses on one lever reset the ratio requirement on the other lever. During choice trials, failure to complete the fixed-ratio 5 within 30 seconds was considered an omission and resulted in initiation of the intertrial interval, during which both levers were retracted and no lights were illuminated. When an infusion was delayed, completion of the ratio illuminated the center white light continuously for the duration of the delay, after which the white light was extinguished and the infusion was initiated, followed by completion of the intertrial interval.

Monkeys were trained to respond on both levers for infusions of remifentanyl. First, responding on one lever delivered 0.32 $\mu\text{g/kg}$ /infusion remifentanyl, whereas responding on the other lever delivered saline. After the monkey responded predominantly on the drug-associated lever (i.e., at least 80% of the total number of completed ratios were completed on the drug lever) for at least one session, the contingencies were reversed such that the lever that previously delivered remifentanyl delivered saline and vice versa. After at least five alternations, two changes in the procedure were implemented that remained in place for the duration of the study. First, the fixed-ratio requirement was increased from 5 to 30; that is, 30 consecutive responses on one lever were required to deliver each infusion. Second, the intertrial interval was increased from 180 to 480 seconds to accommodate a delay between completion of the ratio and delivery of an infusion. When there was no delay, the intertrial interval and infusion pump activation were initiated simultaneously and ran concurrently to ensure that the reinforcer rate (i.e., the number of pump activations per unit time) did not vary with either the infusion duration or reinforcer delay. When an infusion was delayed, the intertrial interval and the delay were initiated simultaneously, with infusion pump activation beginning following the delay. The increase in the intertrial interval required that the number of total possible choice trials presented per session was reduced from 28 to 10 per 100-minute session.

Experiment 1. Dose-effect curves were initially determined by varying the dose of remifentanyl available on one lever (lever A) while saline was available on the other lever (lever B). Designation of a lever as A or B denotes the functional consequences of responding on that lever, that is, delivery of remifentanyl or saline. The same dose of remifentanyl was available within and across sessions until the number of infusions did not vary by more than two for three consecutive sessions. Tests with each dose of remifentanyl were followed by a condition in which only saline was available on both levers, and this condition remained in effect until the number of infusions obtained for three consecutive sessions was equal to or less than half of the mean number of infusions obtained when 0.32 $\mu\text{g/kg}$ /infusion remifentanyl was available. To determine the ascending limb of the remifentanyl dose-effect curve, doses typically were tested in descending order, starting with 0.32 $\mu\text{g/kg}$ /infusion remifentanyl and decreasing to a dose that did not maintain responding above that observed when only saline was available on both levers. The largest dose tested, 1.0 $\mu\text{g/kg}$ /infusion, was tested after the other doses and immediately prior to the start of the second experiment.

Experiment 2. Initially, the same dose of remifentanyl (1.0 $\mu\text{g/kg}$ /infusion) was available on both levers. After responding was stable (i.e., the number of infusions did not vary by more than two for three consecutive sessions), dose-effect curves were obtained by decreasing the dose of remifentanyl on the preferred lever (A), defined as the lever on which a majority of ratios were completed. The dose of remifentanyl was decreased in half-log-unit increments across conditions until the monkey responded on the lever (B) associated with the large dose (1.0 $\mu\text{g/kg}$ /infusion). Each condition remained in effect for at least three sessions and until responding was stable.

The effects of delaying the delivery of a large dose of remifentanyl were studied under similar conditions. Initially, the same dose of remifentanyl (1.0 $\mu\text{g/kg}$ /infusion) was available immediately on both levers. A delay [30, 60, 120, or 240 (SH only) seconds] then was imposed between completion of the response requirement and

delivery of the infusion associated with the preferred lever (B). Thus, monkeys were given a choice between an infusion of 1.0 $\mu\text{g/kg}$ remifentanyl delivered immediately or after a delay. After responding was stable for the immediately available infusion, the dose of remifentanyl to be delivered immediately (lever A) was decreased in half-log-unit increments across successive conditions until the monkey either responded predominantly on the lever associated with the large, delayed dose (1.0 $\mu\text{g/kg}$ /infusion; lever B) or received fewer than five total infusions during choice trials per session for three consecutive sessions. Delays were studied in an irregular order, and the location of the lever associated with the delayed infusion was varied irregularly across tests for each monkey.

Drugs. Remifentanyl hydrochloride (Bioniche Pharma, Lake Forest, IL) was dissolved in 0.9% saline and delivered intravenously. Infusion durations were calculated before each session for each pump based on body weight, the unit dose of remifentanyl, and the infusion rate; infusion duration ranged from 8 to 18 seconds. When monkeys were given a choice between saline and remifentanyl, the infusion duration for saline was matched to the infusion duration for remifentanyl for that session. When saline was available on both levers, infusion duration was matched to the doses available during the most recent condition in which remifentanyl was available. At the end of every session, catheters were flushed and locked with 2.5 ml of heparinized saline (100 units/ml; Hospira, Inc., Lake Forest, IL).

Data Analyses. The number of infusions received from either alternative was taken as the primary measure of choice. Response rates were calculated by dividing the sum of responses on lever A and lever B during choice trials by the total time spent in choice trials. The means of the last three sessions of each condition (i.e., sessions over which responding was considered stable) were plotted as a function of unit dose of remifentanyl. When possible, the dose of remifentanyl on the variable-dose lever (lever A) to occasion 5 of the 10 total infusions available during choice trials (ED_{50}) was interpolated using data comprising the ascending limb of dose-effect curves, defined as the portion of the curve including data ranging from the largest dose that occasioned fewer than 5 infusions to the smallest dose that occasioned more than 5 infusions. For monkey MI, during experiment 1, the smallest dose tested (0.01 $\mu\text{g/kg}$ /infusion) produced an average of 5.3 infusions; therefore, this dose was taken as the ED_{50} . All data analyses were conducted using GraphPad Prism (version 5.04; GraphPad Software, Inc., La Jolla, CA).

Results

Monkeys required an average of 4.3 sessions (range 3–8) to establish lever-pressing for food. During the initial training phase of the study, when drug was available on one lever and saline was available on the other lever, monkeys required an average of 3.5 sessions (median 3, range 1–8) to satisfy the criterion of completing at least 80% of ratios on the drug-appropriate lever for one session following a switch in the lever that was associated with delivery of drug. Thereafter, an average of 4.6 sessions (median 4, range 3–12) was required to satisfy the 3-session stability criterion across all conditions of experiments 1 and 2.

When responding on either lever delivered an infusion of saline [Fig. 1, data above S/S (lever A/lever B)], monkeys received, at most, 4 (range 0–4) total infusions across both levers during choice trials (top panels), and overall response rates during choice trials ranged from 0.4 to 0.5 responses per second (bottom panels). Remifentanyl dose-dependently increased the number of drug infusions delivered and response rate. When a small dose of remifentanyl was available, responding was similar to responding when saline was available on both levers. One monkey (MI) responded at 0.66 responses

Fig. 1. The number of infusions delivered (top panels) and response rates (bottom panels) during choice trials plotted as a function of dose of remifentanyl for experiment 1. (Top panels) Filled circles indicate the number of infusions (saline or remifentanyl) delivered for responding on lever A; triangles indicate the number of infusions received (saline) for responding on lever B. (Bottom panels) Response rates (responses per second). The abscissae indicate the solutions [saline (S) or remifentanyl ($\mu\text{g/kg/infusion}$)] available for self-administration from each lever. Each data point represents the mean ($\pm$ range) from the last three sessions of each condition for each individual monkey, shown across columns.

per second and received 5 infusions of 0.01 $\mu\text{g/kg/infusion}$ remifentanyl (Fig. 1, top and bottom panels). The remaining three monkeys received, at most, 3 infusions of 0.032 $\mu\text{g/kg/infusion}$ remifentanyl and responded at 0.11–0.53 responses per second. When the dose was increased to 0.1 $\mu\text{g/kg/infusion}$, responding on the lever that delivered drug (lever A) increased, with all monkeys receiving, on average, at least 9 infusions. Responding on the saline lever (lever B; Fig. 1, top panels, triangles) remained low with monkeys receiving, on average, 0.7 (range = 0–1) infusions. ED_{50} values for remifentanyl (lever A) were estimated to be 0.01 (MI), 0.05 (MO), 0.04 (SO), and 0.05 (SH) $\mu\text{g/kg/infusion}$. Maximum overall response rates ranged from 1.7 to 5.0 responses per second across monkeys. The average total number of responses per reinforcer during choice trials (responses on lever A plus lever B) during experiment 1 was 30.9 (median 30.0, range 30.0–41.5), indicating that monkeys responded predominantly on one lever during each trial.

During experiment 2, responding on either lever delivered an infusion of remifentanyl. The dose available on one lever (A) varied across conditions, whereas 1.0 $\mu\text{g/kg/infusion}$ remifentanyl was always available on the other lever (B). When monkeys could respond on either lever for immediate delivery of 1.0 $\mu\text{g/kg/infusion}$ remifentanyl, all monkeys responded predominantly on one lever (three responded on the left and one on the right; Fig. 2, filled circles, data above 1.0/1.0). As the dose available on lever A decreased, responding on lever A decreased (Fig. 2, top panels) and responding on lever B increased (Fig. 2, middle panels). When the dose available on lever A decreased to 0.32 $\mu\text{g/kg/infusion}$, two monkeys (MI and MO) began responding predominantly on the other lever (B). Monkeys SO and SH continued to respond predominantly for 0.32 $\mu\text{g/kg/infusion}$ and switched responding

to the other lever when the dose was further decreased to 0.1 $\mu\text{g/kg/infusion}$. ED_{50} values for responding on lever A when both infusions were available immediately were estimated to be 0.60 (MI), 0.36 (MO), 0.18 (SO), and 0.18 (SH) $\mu\text{g/kg/infusion}$; for each monkey, these values were larger than those obtained during experiment 1.

Delaying delivery of 1.0 $\mu\text{g/kg/infusion}$ remifentanyl (lever B) increased responding for smaller, immediately available doses of remifentanyl (lever A), shifting the dose-effect curves leftward (Fig. 2, top and middle panels, open symbols). For monkey MI, delaying delivery of the large dose of remifentanyl by 30 and 60 seconds reduced ED_{50} values to 0.17 and 0.18 $\mu\text{g/kg/infusion}$, respectively, shifting dose-effect curves leftward 4- and 3-fold as compared with when both infusions were available immediately. For monkey SO, the 60-second delay shifted the remifentanyl dose-effect curve 3-fold to the right by reducing responding for immediate delivery of 0.32 $\mu\text{g/kg/infusion}$ remifentanyl. Delaying delivery by 120 seconds reduced ED_{50} values to 0.06, 0.01, and 0.02 $\mu\text{g/kg/infusion}$ and shifted the curves leftward 11-, 34-, and 10-fold in MI, MO, and SO, respectively.

For monkey SH, delays of up to 120 seconds did not substantially change the number of infusions of the smaller dose received (lever A); however, the number of delayed infusions received decreased in a delay-related manner (lever B) from at least 8 infusions to an average of 5.7 infusions. A delay of 240 seconds increased the number of infusions of 0.1 $\mu\text{g/kg/infusion}$ delivered immediately from 0 to 6, reducing the ED_{50} to 0.09, and resulting in a 2-fold shift leftward in the remifentanyl dose-effect curve (Fig. 2, top row, right panel, data above 0.1/1.0).

Response rates (Fig. 2, bottom panels) generally did not vary in relation to reinforcer delay or dose with three possible

Fig. 2. The number of infusions delivered for responding on lever A (top panels) and lever B (middle panels) and overall response rates (bottom panels) plotted as a function of dose of remifentanyl for experiment 2. Filled circles indicate the number of infusions delivered and overall response rates obtained when both infusions were delivered immediately. Open symbols indicate data obtained when monkeys could choose between a small, immediately available dose of remifentanyl available on one lever (A) and a dose of 1.0 $\mu\text{g/kg/infusion}$ remifentanyl available on the other lever (B) after a delay of 30, 60, 120, or 240 seconds. Filled circles above S/1.0 are from Fig. 1. See Fig. 1 for other details.

exceptions. For MI, rates were decreased when 0.032 $\mu\text{g/kg/infusion}$ remifentanyl was available immediately on lever A and 1.0 $\mu\text{g/kg/infusion}$ remifentanyl was available after a 120-second delay on lever B. For MO, rates were decreased when 0.01 $\mu\text{g/kg/infusion}$ remifentanyl was available immediately on lever A and 1.0 $\mu\text{g/kg/infusion}$ remifentanyl was available after a 120-second delay on lever B. Finally, for monkey SH, when 0.32 and 1.0 $\mu\text{g/kg/infusion}$ remifentanyl were available immediately from levers A and B, respectively, response rates were approximately three times higher than when only 1.0 $\mu\text{g/kg/infusion}$ was available on one lever and saline on the other (Fig. 2, data above S/1.0). During experiment 2, the average total number of responses per reinforcer during choice trials was 31.5 (median 31.5, range 30.0–40.0).

Discussion

Drug abusers discount the value of delayed reinforcers more rapidly than individuals who have never used drugs or

former users. The association between delay discounting and drug abuse has been well documented (e.g., Bickel and Marsch, 2001), and enhanced discounting is thought to play a critical role in the development and maintenance of drug abuse as well as other addictive behaviors (Bickel et al., 2012). Because opioid abuse continues to be a significant public health problem, understanding factors that contribute to opioid abuse, such as delay discounting (i.e., impulsivity), will aid both in the identification of risk factors and in the development of more effective treatments. This study examined the impact of delaying the delivery of a large dose of the μ -opioid receptor agonist remifentanyl on choice when the alternative was a smaller, immediately available dose of remifentanyl. Whereas previous work studying the impact of delay on drug self-administration focused almost exclusively on cocaine-maintained behavior (e.g., Woolverton et al., 2007), this study extends the analysis to μ -opioid receptor agonists.

The results of this study indicate that responding maintained by remifentanyl under a concurrent fixed-ratio schedule

is sensitive both to reinforcer magnitude and to delay. Remifentanyl dose-dependently increased responding on the drug lever when responding on the other lever delivered saline. Doses of remifentanyl that maintained responding in the current study (0.1–1.0 $\mu\text{g/kg/infusion}$) are comparable to doses that have previously been reported to maintain lever-pressing in rhesus monkeys (Ko et al., 2002; Woods and Winger, 2002). When the same dose of remifentanyl (1.0 $\mu\text{g/kg/infusion}$) was available immediately on both levers, monkeys responded exclusively on one lever. However, responding on that preferred lever (A) decreased as the dose available on that lever was decreased. Remifentanyl was less potent to maintain responding (on lever A) when a large dose (1.0 $\mu\text{g/kg/infusion}$) was available on lever B as compared with when saline was available on lever B; the remifentanyl dose-effect curve for responding on lever A was shifted 3- to 7-fold rightward for three monkeys and 60-fold rightward in a fourth monkey (MI). These data suggest that the effectiveness of smaller doses of remifentanyl to maintain responding on one lever (A) was diminished by the availability of an alternative source of drug.

Other things being equal, monkeys would be expected to distribute responses evenly across two alternatives when the choice is between the same dose delivered from those alternatives (e.g., Iglauer and Woods, 1974). However, given the tendency of concurrent fixed-ratio schedules to occasion exclusive preferences (Johanson and Schuster, 1975; Galuska et al., 2006), it is not unexpected that monkeys responded on one alternative. For two monkeys, MI and MO, reducing the dose available from the preferred lever shifted responding from that lever to the alternative that delivered the large dose (1.0 $\mu\text{g/kg/infusion}$), consistent with previous data (Galuska et al., 2006). Two other monkeys (SO and SH) continued responding for a smaller dose of remifentanyl (0.32 $\mu\text{g/kg/infusion}$) on one lever (A) despite the availability of the large dose on the other lever (B). Forced trials at the beginning of the session ensured contact with the consequences (e.g., dose) associated with responding on either lever for that session. It is possible that the descending order of dose presentation engendered responding for a smaller dose of remifentanyl despite the availability of a large dose on the alternative.

Choice between two doses of remifentanyl was sensitive to reinforcer delay. Delaying delivery of a large dose of remifentanyl decreased responding for that dose and increased responding for smaller, immediately available doses, resulting in a 2- to 34-fold increase in the potency of remifentanyl delivered immediately to maintain responding. Similarly, delaying delivery of a large dose of cocaine increased responding for smaller, immediately available doses, shifting the dose-effect curve for immediate infusions of cocaine leftward up to 16-fold (Woolverton et al., 2007). Taken together, these data support the view that delaying delivery of a large dose of drug reduces its effectiveness to maintain responding (see also Beardsley and Balster, 1993) and increases the effectiveness of smaller, immediately available doses. Moreover, in monkeys MO and SO, delaying delivery of a large dose increased responding for doses of remifentanyl (0.01 and 0.032 $\mu\text{g/kg/infusion}$) that did not maintain responding above what was obtained with saline during experiment 1 (i.e., when responding on one lever delivered remifentanyl and responding on the other lever delivered saline). Leftward shifts in the remifentanyl dose-effect curve on lever A, when a dose of 1.0 $\mu\text{g/kg/infusion}$ was delayed by 120 seconds (34- and 10-fold,

respectively), exceeded the rightward shifts produced by the availability of 1.0 $\mu\text{g/kg/infusion}$ on lever B (7- and 4-fold, respectively).

A 60-second delay shifted the dose-effect curve slightly rightward in monkey SO, owing primarily to a switch in responding for immediate delivery of 0.32 $\mu\text{g/kg/infusion}$ remifentanyl to responding for delayed delivery of 1.0 $\mu\text{g/kg/infusion}$. However, this small rightward shift was not observed in other monkeys, and it was much smaller than the ≥ 100 -fold leftward shifts in dose-effect curves obtained with longer delays in this and other monkeys.

Allocation of responses across the two alternatives in monkey SH was less sensitive to delay. A delay of 240 seconds only slightly shifted the dose-effect curve maintained by immediate infusions of remifentanyl. The modest shift in the curve might suggest that this monkey was less sensitive than other monkeys to reinforcer delay; however, the overall number of infusions delivered decreased at long delays. That is, not only did delay decrease responding for the large, delayed dose of drug, it only slightly increased the number of infusions of the smaller, immediately available dose. Delaying reinforcement can alter the allocation of behavior (Chung and Herrnstein, 1967) and reduce response rates (Sizemore and Lattal, 1978), but these two effects do not always covary. Shifts in preference might depend upon the reinforcing effectiveness of immediately available alternatives (Maguire et al., 2013). It is possible that, for this monkey, the reinforcing effectiveness of smaller doses of remifentanyl was not increased sufficiently to maintain responding.

The effect of delay on choice in the current study suggests that reductions in reinforcing effectiveness of large doses of drug can significantly enhance responding for smaller doses. Other factors that reduce reinforcing effectiveness, such as increased cost or work requirement, might also be expected to similarly enhance responding for smaller, but less costly, alternatives. Indeed, delaying delivery of the large dose of remifentanyl in this study produced effects on choice similar to the effect of increasing the response requirement (or cost) of a large dose of remifentanyl. In a study using behavioral economic analyses to examine remifentanyl choice (Galuska et al., 2006), monkeys could choose between a small dose of remifentanyl (0.1 $\mu\text{g/kg/infusion}$) delivered contingent upon two responses (fixed ratio 2) and a larger dose of remifentanyl (0.3 $\mu\text{g/kg/infusion}$) delivered contingent upon a range of response requirements. Monkeys responded for the larger dose of remifentanyl up to fixed ratio values of 120 or 240; however, with further increases in the response requirement, monkeys responded predominantly for the small dose. Thus, as with delaying the delivery of a large dose, increasing its cost reduces the effectiveness of that dose to maintain responding and increases the effectiveness of less costly or immediately available smaller doses.

Enhancement of responding for smaller doses of drug in the context of delayed delivery of large doses, in this and previous studies (Woolverton and Anderson, 2006; Woolverton et al., 2007), reflects the enhancement of responding for drug when delivery of alternative food reinforcers are delayed. For example, Woolverton and Anderson (2006) showed that delaying delivery of food increased responding for cocaine, demonstrating that delays can modulate preference in monkeys given a choice between drug and nondrug reinforcers. In a recent study (Maguire et al., 2013), delaying

delivery of food increased responding for immediately available doses of remifentanyl that otherwise (when both food and drug were available immediately) did not maintain responding, resulting in a 2- to 3-fold increase in the potency of remifentanyl to maintain responding. Although drug abusers are more likely to encounter a choice between drug and nondrug reinforcers, the generality of results across experiments using food-drug and drug-drug choice procedures demonstrates the robust effect of delay on drug taking. How the nature of the reinforcer (e.g., food or drug) or the recent drug history of the individual (e.g., currently using drugs or abstinent) modulates the impact of delay on choice remains to be addressed experimentally with these types of procedures. Both factors appear to modulate delay discounting in opioid-dependent individuals (e.g., Giordano et al., 2002); therefore, future research would benefit from continued examination of the impact of delay using choice procedures.

Given that delaying the delivery of drug and nondrug reinforcers can have a profound effect on drug-taking, a better understanding of the impact of delay on drug taking could augment treatment of drug abuse by helping to identify optimal strategies for implementing behavior change. For example, delaying the delivery of alternative, nondrug reinforcers can increase drug-taking under some conditions (Woolverton and Anderson, 2006; Maguire et al., 2013); therefore, strategies aimed at reducing risk of initiation or resumption of drug use after a period of abstinence might be to reduce delays to alternatives. Indeed, the application of behavioral principles has proven effective in developing clinically useful treatments (e.g., see Higgins et al., 2008).

In summary, this study found that delay to reinforcement substantially impacts choice involving different doses of the μ opioid receptor agonist remifentanyl—specifically, that delaying the delivery of a large dose can increase choice of smaller, immediately available doses. Taken together with previous research (Anderson and Woolverton, 2003; Woolverton and Anderson, 2006; Woolverton et al., 2007; Maguire et al., 2013), these results show that delaying the delivery of otherwise preferred drug (e.g., cocaine and remifentanyl) or nondrug (food) reinforcers can enhance the effectiveness of smaller doses of drug to maintain responding. Increases in the effectiveness of smaller doses of drug might increase the probability of drug use, particularly among individuals who are more sensitive to reinforcer delay. Moreover, these studies underscore the importance of taking into account the environmental context in which drug-taking occurs.

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Authorship Contributions

Participated in research design: Maguire, Gerak, France.

Conducted experiments: Maguire.

Performed data analysis: Maguire.

Wrote or contributed to the writing of the manuscript: Maguire, Gerak, France.

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