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Choice between delayed food and immediate oxycodone in rats

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Abstract

Rationale—The choice to seek immediate drug effects instead of more meaningful but delayed rewards is a defining feature of addiction.

Objectives—To develop a rodent model of this behavior, we allowed rats to choose between immediate intravenous delivery of the prescription opioid oxycodone (50 µg/kg) and delayed delivery of palatable food pellets.

Results—Rats preferred food at delays up to 30 s, but they chose oxycodone and food equally at 60-s delay and preferred oxycodone over food at 120-s delay. Comparison of food-drug choice, food-only, and drug-only conditions indicated that food availability decreased drug intake, but drug availability increased food intake. In the food-only condition, food was effective as a reinforcer even when delayed by 120 s. Pre-session feeding with chow slowed acquisition of food and drug self-administration, but did not affect choice. To establish procedures for testing potential anti-addiction medications, noncontingent pretreatment with oxycodone or naltrexone (analogous to substitution and antagonist therapies, respectively) were tested on a baseline in which oxycodone was preferred over delayed food. Naltrexone pretreatment decreased drug intake and increased food intake. Oxycodone pretreatment decreased drug intake, but also produced extended periods with no food or drug responding.

Conclusions—These findings show that the contingencies that induce preference for drugs over more meaningful but less immediate rewards in humans can be modeled in rodents, and they suggest that the model could be useful for assessing the therapeutic potential of treatments and exploring the underlying behavioral and neural mechanisms involved in addiction.

Keywords

Addiction; animal models; behavioral economics; concurrent choice; delay discounting; impulsivity

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Compliance with ethical standards

The facilities were fully accredited by the American Association for the Assessment and Accreditation of Laboratory Animal Care. Procedures were approved by the Animal Care and Use Committee of the National Institute on Drug Abuse Intramural Research Program and followed the guidelines of the National Research Council (2011).

Conflict of interest

The authors declare no conflicts of interest.

INTRODUCTION

It has long been recognized that delay weakens the effects of reinforcement (Thorndike 1911) and that people discount the value of goods that will not be received until a later date (Smith, 1759). Along with cost, value and availability, delay is one of the main factors that influence the choice to seek one reinforcer instead of another (Domjan 2009; Heinz et al. 2012). The effects of delay on choice behavior are readily studied with concurrent schedules in which one response produces immediate reinforcement and a different response produces delayed reinforcement. In many such studies, as the length of the delay is increased, preference switches from a large delayed reinforcer to a small immediate reinforcer. These procedures have been used extensively in both human and nonhuman subjects, and the results are generally similar across species (Bickel and Johnson 2003).

Immediate reinforcement is sometimes preferred over delayed reinforcement, even when the delayed reinforcer is larger or more meaningful (i.e., when it is demonstrably more beneficial and would be preferred if it were not delayed). Such preference is considered a form of impulsivity relevant to addiction and other psychiatric disorders (Bari and Robbins 2013; de Wit 2009; Perry and Carroll 2008). In the case of drugs, the relationship between this kind of impulsivity and addiction appears to go both ways: drug exposure can increase impulsive choice, and individuals who show signs of impulsivity prior to initiating drug use are more likely to become regular users (Harvey-Lewis et al. 2012; Kirby et al. 1999; Mendez et al. 2010; Perry et al. 2005).

Since discounting of meaningful but delayed reinforcers might play an important role in addiction, it makes sense to develop animal models that involve a choice between immediate delivery of drug and delayed delivery of food. In rhesus monkeys, this has been achieved with cocaine (Huskinson et al. 2015; see also Woolverton and Anderson 2006) and the μ -opioid agonist, remifentanyl (Maguire et al. 2013). In these studies, when immediate food was preferred under baseline conditions, monkeys switched to preferring drug when food was delayed by 60–240 s.

Woolverton and Anderson (2006) remarked that nonhuman primates are "uniquely suited" to this kind of research, but that "methodological streamlining is indicated." Nonhuman primates are phylogenetically close to humans, and they can be tested over long periods, which facilitates parametric testing of delay, dose and food amount within subjects. However, rodents also offer many advantages. They are well-suited for studies that involve nonreversible treatments or that require naive subjects or large numbers of subjects. Rodent research is also less expensive, and many laboratories have facilities for drug self-administration in rats. Therefore, in the present study we evaluated the feasibility of using rats to study choice between drugs and delayed food. We manipulated parameters that could influence choice, such as delay, timeout, unit dose and hunger state. We also established procedures for testing potential anti-addiction medications on a baseline where immediate drug is preferred over delayed food. Although the general procedure should be applicable to any drug self-administered by rats, oxycodone was chosen for this study because of its relevance to the increasingly alarming problem of prescription opioid abuse (Kolodny et al. 2015).

METHODS

Subjects

Experimentally-naive male Sprague–Dawley rats ($n=20$; Charles River, Wilmington, MA), 3–4 months old at the start of the study, were single housed on a 12-h light cycle with experiments conducted in the light phase. Food was restricted to 15–20 g/day of laboratory chow in all rats. To assess the effects of hunger state on choice, throughout the study "hungry" rats were fed 15 minutes after the daily training session, and "sated" rats were fed 3 hours before the session. Body weight (mean $\pm$ s.e.m.) did not differ significantly between hungry (358 ± 17 g) and sated rats (339 ± 26 g). One week before self-administration training, a jugular-vein catheter and subcutaneous backmount were implanted as described earlier (Panlilio and Schindler 2000). If a catheter lost patency, a new jugular or femoral-vein catheter was implanted to allow completion of the study. Catheters were flushed daily with 0.1 ml of heparin (200 USP units/ml) and gentamycin (0.4 mg/ml).

Apparatus

Experimental chambers (30 x 24 x 29 cm; Coulbourn Instruments, Allentown, PA) in sound attenuation chests had a central amber cuelight on the wall above two nosepoke holes that could be lit from within. Food pellets (45 mg, ~58% sugar by weight, 19% protein and 6% fat by proximate analysis; Product #F0021; Bio-Serv, Frenchtown, NJ) were delivered between the nosepoke holes. Intravenous (IV) oxycodone was delivered at a rate of 3.2 ml/min over ~2 s. Drug tubing passed through a metal spring connected to the backmount. Experiments were controlled with Med-PC software (Med Associates, St Albans, VT). Oxycodone hydrochloride (μ -opioid agonist) and naltrexone hydrochloride (opioid antagonist) (Sigma-Aldrich, Natick, MA) were dissolved in saline. The IV oxycodone dose was 50 μ g/kg/inj for all conditions except acquisition training and the unit-dose experiment. Volumes were 1 ml/kg for IP and SC injections and ~0.1 ml for IV.

General procedure

Overview—Rats were trained 5–7 days/week. All sessions lasted for 2 hours or 100 food pellets. Since the sequence of initial exposure could potentially affect preference, 10 rats (4 hungry and 6 sated) were trained with food first, and 10 rats (3 hungry and 7 sated) with drug first. The phases of the study are outlined in Table 1.

Basic training schedule—When a hole was lit, a response in that hole immediately turned off all hole lights and turned on the cuelight for a period to be referred to as the "timeout" period. Depending on the schedule and the side of the hole (left or right), the timeout period included delivery of an immediate oxycodone injection (inj), a delayed food pellet, or no primary reinforcement. After the timeout, the hole light turned back on and the cuelight turned off, starting the next trial. The stated timeout duration includes the delay or injection time; for example, a 5-s delay with a 20-s timeout means that food was delivered 5 seconds after the response, and the next trial started 15 seconds after food delivery. Timeout duration was always the same for food and drug within a session. Responding in an unlit hole had no programmed effect at any time, including the delay period. However, if responding occurred during timeout after food or drug was delivered, and if the first

response in a lit hole during the next trial was not in the same hole as the last timeout response, two consecutive responses were required in a lit hole to enter the next timeout period ("changeover" contingency). Holes remained lit until a response occurred or the session ended.

Schedule variations—Both holes were always available. "One-hole" and "two-hole" conditions refer to how many holes were lit during trials. One-hole conditions were used in acquisition training. Two-hole conditions were used for food-only and drug-only conditions, with the "active" hole producing timeout plus primary reinforcement, and the "inactive" hole producing only timeout. In "choice" conditions, both holes were lit; responding in the right hole produced timeout plus delayed food, and responding in the left hole produced timeout plus immediate drug.

Food-first training

Response-acquisition and one-hole food training—Food-first rats acquired nosepoke responding under a one-hole food schedule with the right hole active and with timeout plus food also delivered automatically (on a variable-time schedule) about once per minute, until at least 25 reinforced responses occurred for two consecutive sessions. Then, one-hole food training continued without automatic delivery until there were two consecutive sessions with 100 reinforced responses and at least 90% of responses in the lit hole (discrimination criterion). All food reinforcement prior to the choice-testing phase was 5-s delay and 20-s timeout.

Two-hole food training and reversals—Two-hole food training was then conducted with the right hole active. When the 90% discrimination criterion was met, the side of the active hole was reversed. To foster sensitivity to the current outcome associated with the response, reversals were repeated until each food-first rat met criterion five times under the two-hole food schedule: three times with the right hole active and two times with the left hole active.

Oxycodone training—After reversal training with food, food-first rats were trained with oxycodone (100 µg/kg/inj) under a one-hole drug schedule with the left hole active. The dose was decreased to 50 µg/kg/inj after 3 sessions. One-hole drug training continued until there were at least 10 injections/session and 90% discrimination for two consecutive sessions. However, the 90% discrimination criterion was waived for all sated rats in the food-first group because they were not advancing toward that criterion after more than 12 sessions. Food-first rats were then given 2–5 days of saline extinction and 4 days with a two-hole oxycodone schedule before starting choice testing.

Drug-first training

Response-acquisition and oxycodone training—Drug-first rats acquired nosepoke responding under a one-hole drug schedule (20-s timeout, left hole active) at a dose of 100 µg/kg/inj, decreased to 50 µg/kg/inj after 4 sessions. When the 10 inj/session and 90% discrimination criteria had been met for two consecutive sessions under the one-hole drug schedule and then the two-hole drug schedule, rats were moved directly to the choice

schedule. Two sated rats did not immediately acquire food responding, so they were given one-hole food training with automatic pellet delivery until they reached the 90% discrimination criterion (4–7 days), then returned to the choice schedule.

Choice testing

Initial delay curves—Choice testing started with 5-s food delay and 20-s timeout. Then, delay curves were obtained by increasing the food delay and timeout in steps as shown in Table 1. Each delay value was maintained until the percentage of responses in the food hole did not differ by >10 percentage points for two consecutive sessions, with no upward or downward trend. To avoid satiation, sessions were ended early if 100 pellets were obtained, but this could only happen when the timeout was 20 or 45 s; longer timeouts inherently limited the 2-h session to a maximum of 97 trials at 75-s timeout and 49 trials at 150-s timeout.

Post-choice single-reinforcer tests—After the initial delay curves were determined, all rats were tested with a drug-only condition and then a food-only condition, with the longest timeout (150 s) and food delay (120 s) values that had been used during choice testing.

Delay curves with fixed timeout—Since delay and timeout values had been confounded in the initial determination (see Table 1), delay curves were redetermined with the timeout held constant at 150 s (a value long enough to encompass all delay values). Delay was manipulated under the choice schedule and the food-only schedule, in mixed order across rats.

Timeout curves with fixed delay—Next, to assess the effects of long vs. short timeout values (which can influence choice-related factors such as opportunity cost), food delay was held constant at 5 s while the timeout was varied between 20 and 150 s. This was performed under the choice, food-only, and drug-only schedules, in mixed order.

Unit dose and pretreatment manipulations—Finally, three pharmacological experiments were conducted in mixed order under choice conditions in which oxycodone was preferred over food (120-s delay, 150-s timeout). IV oxycodone unit-dose experiment: doses of 0, 12.5, 25, 50, 100 and 200 µg/kg/inj were each tested for two consecutive sessions. Subcutaneous (SC) naltrexone pretreatment experiment: doses of 0, 0.1, 0.3, 1, 3 and 10 mg/kg were given 15 minutes before the session. Intraperitoneal (IP) oxycodone pretreatment experiment: doses of 0, 0.5, 1, 2 and 4 mg/kg were given noncontingently 5 minutes before the session. Naltrexone and IP oxycodone were tested up to 2 times/week, when percent choice was within 10 percentage points during the two previous baseline sessions. The order of dosing in each experiment was counterbalanced across rats.

Data analysis

Analysis was performed using Proc Mixed (SAS Institute, Cary, SC). The Tukey-Kramer procedure was used 1) to compare each pair of points within a given delay, timeout or dose curve, and 2) to compare between curves for each pair of points at a given level of delay,

timeout or dose. Choice was measured as percentage of responses (normalized by arcsine-root transformation) in the food hole when both holes were lit (i.e., including reinforced responses and nonreinforced changeover responses, but not timeout responses). After initial training, results for food-first and drug-first rats in the hungry group did not differ significantly and were therefore combined. Similarly, for all experiments after post-choice single-reinforcer testing, there were no significant differences related to hunger state or order of training, so data were collapsed across these conditions. The efficiency of responding was analyzed to better understand the effects of timeout on intake, by controlling for differences in the maximum number of trials/session across sessions with different timeout values. For short timeouts (20–45 s), where the session ended if 100 pellets or injections were obtained, efficiency was calculated as the number of preferred reinforcers, expressed as a percentage of 100. For long timeouts (75 s or longer), where timeout itself limited the maximum number of trials per session, efficiency was calculated as the number of trials completed, expressed as a percentage of the maximum allowed by the schedule parameters. Efficiency data for short and long timeouts were analyzed separately, except for the initial delay experiment, where timeout and delay were not independent.

RESULTS

Pre-choice training

Sated rats took longer than hungry rats to meet food-training criteria in early training (Fig. 1A) [Feeding $\times$ schedule: $F(6,47)=2.5$, $P<.04$], but did not differ from hungry rats during the final two reversals. Sated rats also took longer than hungry rats to meet drug-training criteria (Fig. 1B), regardless of whether they were trained with food first or drug first [Feeding: $F(1,16)=10.6$, $P<.005$].

Initial choice testing

Initial delay curves—All rats strongly preferred food to oxycodone when food was delayed by 5 s, but with each increase in delay their choice shifted significantly toward oxycodone (Fig. 2A) [Delay: $F(4,63)=22.7$, $P<.0001$]. Choice was not significantly affected by hunger state or initial-training conditions (connected points in Figs. 2B, 2C, 2D), so delay-curve data were collapsed across groups for paired comparisons (Fig. 2A). Nonreinforced changeover responses were infrequent (mean $\pm$ s.e.m. changeovers/session = 4.2 ± 0.4 in the food hole and 4.8 ± 0.5 in the drug hole).

Pre-choice and post-choice single-reinforcer tests—All rats consistently chose the active hole (which produced timeout plus food or drug) over the inactive hole (which only produced timeout), both before and after choice testing, even with long delay and timeout values (unconnected points in Figs. 2B, 2C, 2D) [Group $\times$ hole $\times$ time: $F(2,9)=7.4$, $P<.02$]; since this significant interaction involved group, the single-reinforcer conditions were not collapsed across groups for paired comparisons. Hungry rats did not differ from sated rats during single-reinforcer testing, except during pre-choice drug-only training (Fig. 2D), when sated rats trained with food first did not meet the 90% discrimination criterion.

Intake during initial choice testing and single-reinforcer tests—As the food delay was lengthened in initial choice testing, food intake decreased and drug intake increased (connected points in Fig. 3A) [Delay x reinforcer: $F(4, 64)=65.9$, $P<.0001$]. During food-only tests (unconnected points with x-marks in Fig. 3A), food intake was higher during pre-choice testing (5-s delay, 20-s timeout) than during post-choice testing (120-s delay, 150-s timeout) [Schedule x hole x time: $F(1,3)=120.4$, $P<.002$]. Food was still reinforcing at the long delay, since timeout with delayed food was chosen more than timeout without delayed food (food hole vs. drug hole in post-choice food-only testing, Fig. 3A). In drug-only testing (unconnected points with dots in Fig 3A), drug intake did not differ between pre-choice and post-choice testing. However, the availability of 120-s delayed food decreased drug intake [Fig 3A, choice condition at longest food delay (rightmost square in delay curve, ~20 inj/session) vs. post-choice drug-only condition (rightmost dotted square, ~30 inj/session): $t(13)=4.5$, $P<.003$]. All these effects were consistent across groups (Figs. 3B, 3C, 3D).

Independent timeout and delay manipulations

Isolated effects of delay on choice—With timeout duration held constant, choice between food and drug was determined by the food delay [Schedule x delay: $F(4, 42)=8.5$, $P<.0001$], producing a delay curve (Fig. 4A, circles) similar to the initial curve (Fig. 2A). Preference for oxycodone at the 120-s delay was stronger in the second determination, but this difference was not due to timeout duration, which was 150 s at this delay for both curves. Delay had no effect on response allocation when only food was available (Fig. 4A, triangles).

Isolated effects of timeout on choice—With delay held constant (Fig. 4B), response allocation was determined by schedule (i.e., whether food, drug or both were available) [$F(2, 23)=417.0$, $P<.0001$], but not by timeout duration. The percentage of responses in the food hole was low in the drug-only schedule (Fig. 4B, downward-pointing triangles) and high in the food-only and food-drug schedules (Fig. 4B, circles and upward-pointing triangles), with a slight but significant difference between the latter two conditions; however, all three of these functions were flat across the full range of timeout values.

Isolated effects of delay and timeout on intake—Food delay decreased food intake (Fig. 4C, black squares) and increased drug intake (Fig. 4C, black diamonds) when timeout value was held constant [Schedule x delay x hole: $F(4,42)=40.1$, $P<.0001$]. These results replicated the initial results (Fig. 3A), but with drug intake surpassing food intake at the longest delay; this made the choice-schedule curves in Fig. 4C more symmetrical than Fig. 3A, where timeout limited intake at long delays but not at short delays. When timeout duration was varied and delay was held constant, food intake decreased as a function of timeout in both the food-drug choice and food-only schedules (Fig. 4D, black and gray squares), with a sharper decline under the food-only condition [Schedule x delay x hole: $F(8,89)=18.6$, $P<.0001$]. Drug intake was not significantly affected by timeout value in any schedule (food-drug choice: Fig. 4D, black diamonds; drug-only: Fig. 4E, outlined gray diamonds).

Interactive effects of food and oxycodone availability on intake—The concurrent availability of 5-s delayed food decreased drug intake (Fig. 4D, gray diamonds) compared to when only drug was available (Fig. 4E, outlined gray diamonds). The availability of 120-s delayed food also decreased drug intake slightly [drug-only condition in timeout manipulation (Fig. 4E, rightmost outlined gray diamond; ~30 inj/session) vs. choice condition in delay manipulation (Fig. 4C, rightmost black diamond; ~25 inj/session): $t(10)=2.3$, $P<.05$]. In contrast, the availability of oxycodone increased food intake, at least when the delay was short and the timeout was long; this was seen in the delay manipulation (Fig. 4C, black squares vs. gray squares, at delays of 5 s and 15 s) and in the timeout manipulation (Fig. 4D, black squares vs. gray squares at timeouts longer than 45 s).

Efficiency of responding—With the food delay held constant at 5 s, rats obtained 99% of available pellets in the choice (Fig. 5D) and food-only (Fig. 5E) conditions at the 20-s timeout, but they only obtained 64% in the food-only condition at the 45-s timeout (Fig. 5E) [Dark bars in Figs. 5D, 5E and 5F, schedule x timeout: $F(2,23)=29.9$, $P<.0001$]. For timeouts of 75 s and longer, efficiency was much lower when only food was available (~50%; light bars in Figs. 5C and 5E) compared to when food and drug were both available (~85%, light bars in Figs. 5B and 5D) [Light bars in Figs. 5D, 5E and 5F, schedule x timeout: $F(4,44)=5.5$, $P<.002$] [Figs. 5B and 5C, schedule x delay: $F(4,42)=3.5$, $P<.02$]. When food and drug were both available with long timeouts (Fig. 5B), efficiency was high at short delays but slightly lower at long delays. Efficiency was also slightly decreased at the longest delay-timeout combination (120-s delay, 150-s timeout) in the initial delay manipulation [Fig. 5A, delay: $F(4,76)=23.4$, $P<.0001$]. In the drug-only schedule (Fig. 5F), efficiency was low at timeout values of 75 s and below, but increased at the 120-s and 150-s timeouts.

Unit-dose and pretreatment manipulations

IV oxycodone dose manipulation—All unit doses of oxycodone were preferred over 120-s delayed food (Fig. 6A), but choice approached 50% when IV saline was substituted for oxycodone for two sessions [Dose: $F(5, 50)=5.5$, $P<.0004$]. The number of injections (Fig. 6B) varied as a function of dose [Dose x hole: $F(5, 50)=22.1$, $P<.0001$], decreasing at 100 and 200 $\mu\text{g/kg/inj}$ compared to the 50- $\mu\text{g/kg/inj}$ baseline, but injection rates were higher than food rates at all doses. Saline substitution decreased injection rates and increased food rates. During the unit dose and pretreatment manipulations, baseline food intake was slightly lower than during the two delay-curve determinations (120-s delay conditions in Figs. 3 and 4C), but baseline drug intake was about the same.

SC naltrexone pretreatment—All doses of naltrexone shifted the choice measure from oxycodone preference to near-equal choice of oxycodone and food (Fig. 6C) [Naltrexone dose: $F(5,63)=8.3$, $P<.0001$], similar to what was seen with IV saline substitution (Fig. 6A). Naltrexone decreased oxycodone intake and increased food intake (Fig. 6D) [Dose x hole: $F(5,63)=6.8$, $P<.0001$].

IP Oxycodone pretreatment—Noncontingent treatment with oxycodone did not significantly affect the choice measure (Fig. 6E) (Dose: $P=.77$), but reduced drug intake

(Fig. 6F, black diamonds) [Hole x dose: $F(4,35)=9.8$, $P<.0001$]. Unlike naltrexone, oxycodone pretreatment increased the latency to the first response of the session (Fig. 6E inset) [Oxycodone dose: $F(4,35)=9.4$, $P<.0001$], and these latencies were ~50 minutes at the highest dose. To examine post-latency behavior, adjusted food and drug intake were calculated based only on the period of time after the first response in each session (Fig. 6F, upward and downward gray triangles); only the highest dose of oxycodone pretreatment decreased drug intake after the initial period of nonresponding [Dose x hole: $F(4,35)=3.9$, $P<.01$].

DISCUSSION

Rats preferred food over oxycodone when the delivery of food was slightly delayed, consistent with earlier studies of food-drug choice in which immediate food was found to be prepotent as a reinforcer in rodents (Ahmed, 2010; Cantin *et al.*, 2010; Caprioli *et al.*, 2015; Madsen and Ahmed, 2015; cf., Kerstetter *et al.*, 2012; Thomsen *et al.*, 2013). However, rats progressively switched to preferring oxycodone when the food delay was increased. This finding is consistent with studies in which nonhuman primates were given concurrent access to drugs and delayed food (Huskinson *et al.*, 2015; Maguire *et al.*, 2013; Woolverton and Anderson 2006), or when humans were asked to choose between drugs and delayed money (Bickel *et al.*, 2011; Mitchell 2004b). The present findings support the hypothesis that delay discounting can influence the choice to seek drugs instead of more meaningful reinforcers (Bickel *et al.*, 2014; de Wit 2009; Perry and Carroll 2008), and they suggest that choice between immediate drug and delayed food in rats can be used to model this aspect of addiction.

Lenoir *et al.* (2007) allowed rats to choose between cocaine delivered immediately and saccharin delayed by up to 18 s, to test the possibility that rats' tendency to prefer sweet substances might be due to taste having a more immediate reinforcing effect than intravenous drugs. They found that choice of cocaine increased slightly at saccharin delays of 12–18 s, but that saccharin was still preferred. In the present study, choice of oxycodone increased slightly at food delays of 15 s, but food and oxycodone were chosen equally at 60-s delay, and oxycodone was preferred at 120-s delay. Rhesus monkeys also switched from food to drug preference when food delays were 60 s or longer (Maguire *et al.*, 2013; Woolverton and Anderson 2006). Putting these findings in perspective, previous delay-discounting studies have typically shown that delays of seconds or minutes in animals have effects comparable to days or months in humans (Bickel and Johnson 2003; Mitchell 2004a).

Consistent with the hypothesis that alternative forms of reinforcement can decrease drug use, concurrent availability of food decreased oxycodone intake, even when food was delayed and oxycodone was preferred. In contrast, concurrent availability of oxycodone increased food intake, at least when the food delay was short and the timeout was long. This effect is consistent with the recent finding that rats' choice between saccharin and heroin is influenced by orexigenic effects of heroin (Vandaele *et al.*, 2016). When oxycodone was not available, the food hole was strongly preferred over the inactive drug hole, even when food was delayed; this indicates that delayed food was reinforcing, and that the switch from food

preference to oxycodone preference when food was delayed was due to discounting of the value of food relative to drug, not to extinction of food responding.

Timeout duration could potentially affect both choice and intake under concurrent schedules. For example, long timeouts can impose opportunity cost by limiting the number of reinforcers that can be obtained within a session. Timeout did not affect choice in the present study, but it should be noted that the longest timeout value (150 s) was shorter than the 10-min intertrial interval used in many food-drug choice experiments in rats (Cantin et al. 2010; Caprioli et al. 2015; Kerstetter et al. 2012; Lenoir et al. 2013; Vandaele et al. 2016). Timeout did have an interesting effect on intake in the food-only schedule: when the timeout was 75 s or longer, only ~50% of available reinforcers were obtained (i.e., fewer trials were completed). Under these conditions, timeout constituted a signaled period of nonreinforcement and probably decreased motivation and attention, making it less likely that a response would occur immediately when the next trial began (Ferster and Zimmerman 1963). In the drug-only schedule, long timeouts actually increased the efficiency of responding, probably because rats tend to pause after each self-injection of opioids and other drugs (Panlilio et al. 2003); since the average interinjection interval was ~185 s under the drug-only schedule at all timeout values, responding immediately after a timeout would have been unlikely at the 20-s timeout value, but increasingly likely at longer values.

As in most studies of delay discounting, choice of delayed food produced an immediate visual cue that presumably facilitated reinforcement by bridging the temporal gap (Mazur 1997). However, it is notable that the relationship between the cue and reinforcement was conditional: responding in an illuminated hole produced the same visual cue under all conditions, regardless of whether food, drug or neither was delivered in the presence of the cue. Under these conditions, the fact that rats were sensitive to delay and to changes in food and drug availability shows that their choice behavior was based on comparisons between the currently-available options, and in this sense might be analogous to decision making in humans.

Hunger state can alter the effectiveness of food reinforcement (Hayashi and Wirth 2012; Murphy et al. 2003) and drug reinforcement (Carroll and Meisch 1984; Kerstetter et al. 2012). Furthermore, palatable food can affect endogenous opioid signaling, and opioid drugs can affect feeding (Gosnell and Levine 2009). All rats in the present study were food restricted, but rats that were fed after the session instead of before the session were faster to meet training criteria for both food and oxycodone self-administration. Thus, with respect to response acquisition, post-session feeding had effects similar to food restriction, increasing sensitivity to drug reward, possibly as a result of overlap between motivational circuitry involved in food reward and drug reward (Carr 2007; Sevak et al. 2008). However, after food and drug responding had been acquired, feeding condition had no noticeable effect on behavior. In this respect, our results are similar to those of Ferguson and Paule (1995), who found that pre-session vs. post-session feeding had surprisingly little effect on already-established food responding. Pre-session feeding with chow also failed to affect choice between sweet food and nicotine in an earlier study, even though it decreased nicotine self-administration in a drug-only condition (Panlilio et al. 2015). The fact that pre-session feeding with chow did not affect choice between food and oxycodone suggests that the

motivation driving choice of food in these rats was specific to sweet pellets (Dickinson et al. 1996).

Changing the unit dose of oxycodone affected the number of injections/session, but it did not diminish the preference for oxycodone over 120-s delayed food. This dose range represents the peak and descending limb of the dose-response curve in rats trained in our lab under a simple five-response fixed-ratio schedule with 20-s timeout (data not shown). Negus (2006) studied heroin-food choice in rhesus monkeys using a procedure where neither reinforcer was delayed, but the unit dose of heroin was varied within the session. Under these conditions, choice of heroin increased as a sigmoidal function of unit dose. In contrast, baboons that were allowed to choose between immediate fixed-dose heroin and immediate food in eight daily trials with long intertrial intervals chose heroin less frequently at higher unit doses (Griffiths et al. 1981). Together, these findings suggest that the effects of unit dose on food-drug choice are highly dependent on the testing conditions. Nonetheless, the fact that rats continued to prefer oxycodone over delayed food across the full range of reinforcing doses suggests that a treatment that effectively decreases the potency of oxycodone only partially would not shift preference toward delayed nondrug reinforcers.

Choice models are underutilized for the study of addiction therapies (Banks and Negus 2012; John et al. 2015; Nader and Banks 2014). In our model, naltrexone effectively eliminated the preference for oxycodone, due to both a decrease in oxycodone responding and an increase in food responding. Thus, blocking the effects of oxycodone at opioid receptors produced results that closely resembled acute extinction of oxycodone; in both cases, intravenous intake decreased, but was not surpassed by food intake. Negus (2006) also found that the opioid antagonist naloxone increased choice of immediate food vs. immediate heroin in rhesus monkeys. In baboons, Griffiths et al. (1975; 1981) found that naloxone increased choice of immediate heroin over immediate food, but they suggested this might be an extinction burst that would subside if naloxone treatment were continued.

Subchronic treatment with noncontingent methadone or morphine decreased heroin choice in opioid-dependent baboons (Griffiths et al. 1975; 1981). Negus (2006) found that methadone had little or no effect on choice behavior when monkeys were not opioid dependent, but it prevented withdrawal-induced increases in heroin choice when monkeys were dependent. In our rats, which showed no signs of dependence, pretreatment with noncontingent oxycodone dose-dependently decreased oxycodone intake. Notably, this decrease was due largely to increases in the amount of time that passed before the first response of the session. It is unclear whether this period of nonresponse was due to drug satiety, sedation, or some other effect of oxycodone, but these doses should not have produced motor impairment (Meert and Vermeirsch 2005).

Conclusion

Addiction presumably arises from an interaction between genetic predisposition, previous experience, and contingencies of reinforcement that exist in the individual's current environment. Delay of reinforcement is a powerful determinant of behavior in humans and in animal models. Delay discounting tends to have a stable, almost trait-like quality in

humans, but it is still amenable to change, and this offers an avenue for understanding how the process can go awry and how it can be improved through therapeutic intervention (Koffarnus et al. 2013). This suggests that the delineation between impulsive addict and nonimpulsive user might represent a continuum rather than a dichotomy. Rats tend to prefer sweet food over drugs, and this can be used to advantage, for example as a model of voluntary abstinence from drug use (Caprioli et al. 2015). However, the present study shows that it is also possible to obtain a range of preferences between food and drug in rats by parametrically varying the delay to food delivery. This procedure could provide a useful model of the conditions that lead to a preference for the immediate effects of drugs over delayed but more meaningful rewards.

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Figure 1.

Number of sessions (mean $\pm$ s.e.m.) required to meet training criteria in hungry and sated groups trained with food first or drug first. **A:** Food training. **B:** Oxycodone self-administration training. "One-Hole" and "Two-Hole" refer how many holes were illuminated, as described in the Methods. "Right" or "Left" indicates which hole produced primary reinforcement. "Acquisition" refers to one-hole food training with additional automatic food delivery. In A, * indicates significant difference between hungry ($n=4$) and sated groups ($n=6$) within the same phase of training. In B, * indicates significant difference between hungry ($n=4$ trained with food first and 3 trained with drug first) and sated ($n=6$ trained with food first and 7 trained with drug first) groups, collapsed across food-first and drug-first conditions. Significant differences in all figures are $P<.05$.

Figure 2.

Initial delay-discounting curves showing choice (percentage of responses in the food hole) as a function of food delay in the food-drug choice schedule (connected points). **A:** All rats combined ($n=19$). **B:** Hungry group ($n=6$). **C:** Sated group trained with drug first ($n=7$). **D:** Sated group trained with food first ($n=6$). Unconnected points in B, C and D show percentage of responses in the food hole during single-reinforcer tests under four conditions: 1) food-only schedule with 5-s delay and 20-s timeout prior to choice testing; 2) food-only schedule with 120-s delay and 150-s timeout after choice testing; 3) drug-only schedule with 20-s timeout prior to choice testing; and 4) drug-only schedule with 150-s timeout after choice testing. * differs from all other points in the curve. # differs from all other food-only and drug-only points. In addition, every drug-only point differs from every food-only point.

Figure 3.

Food and oxycodone intake as a function of food delay during the initial determination of delay-discounting curves with the food-drug choice schedule (same sessions as Fig. 2). **A:** All rats combined. **B:** Hungry group. **C:** Sated group trained with drug first. **D:** Sated group trained with food first. Unconnected points show food and drug intake in single-reinforcer tests under the four conditions described in the caption of Fig. 2. # food-hole vs. drug-hole difference within the same schedule; within the food hole, # also indicates difference between pre-choice food-only condition vs. post-choice food-only condition. * difference within curve (Food: * differs from each other delay; Drug: * differs from 5-s delay). For the inactive hole in food-only and drug only conditions, "reinforcers" refers to responses that produced timeout periods with no food or drug delivery. For food-only and drug only conditions, respectively, "drug hole" and "food hole" refer to the outcome that was associated with that hole in the choice condition.

Figure 4.

Choice and intake during experiments in which food delay and timeout duration were manipulated independently. **A:** Percentage of responses in the food hole during food-drug choice and food-only conditions with delay varied between sessions and timeout held constant at 150 s (n=14). **B:** Percentage of responses in the food hole during food-drug choice, food-only and drug-only conditions with timeout duration varied across sessions and delay held constant at 5 s (n=16). **C:** Intake during food-drug choice and food-only conditions in the same sessions depicted in panel A. **D:** Intake in food-drug choice and food-only conditions for the same sessions depicted in panel B. **E:** Intake in drug-only condition for the same sessions depicted in panel B. * difference within curve. # difference between food and drug holes within food-drug choice or within single-reinforcer condition at same delay and timeout; also, in panels D and E: drug hole in drug-only schedule vs. drug hole in food-only schedule at all timeout values, and food hole in food-only schedule vs. food hole in drug-only schedule at all timeout values. § difference between food-drug choice and

single-reinforcer condition within same delay or timeout. §§ difference between all three conditions, collapsed across timeouts. (Details for within-curve differences marked by * are as follows. Panel A: 120 vs. all others, 60 vs. all others except 30, 30 vs. 5. Panel C, drug hole in choice schedule: 60 vs. 5, 120 vs. all others. Panel C, food hole in choice schedule: 60 vs. 5 and 15, 120 vs. all others. Panel D, food hole in food-only schedule: all pairs except 120 vs. 150. Panel D, food hole in choice schedule: 120 vs. 20 and 45; 150 vs. 20, 45 and 75.) The scale of the ordinate is enlarged to show detail in panel C, where the maximum possible number of reinforcers under all conditions was 49. For the inactive hole in food-only and drug-only conditions, "reinforcers" and "intake" refer to timeout periods with no food or drug delivery.

Figure 5.

Efficiency of responding during sessions with short timeouts (20–45 s; dark-shaded bars) and long timeouts (75–150 s; light-shaded bars) in the initial delay-curve determination (A), the delay manipulation with fixed timeout (B and C), and the timeout manipulation with fixed delay (D, E and F). Data are from the same sessions as Figs. 3A, 4C, 4D and 4E. \$ differs from the choice condition at the same delay or timeout value. * differs from 5-s delay within panel A, from 5-s and 15-s within panel B, from the 20-s timeout within panel E, or from the 75-s timeout within panel F. # drug-only differs from the food-only condition at the same timeout value.

Figure 6.

Choice and intake during unit-dose and pretreatment manipulations under a baseline where oxycodone was preferred. **A:** Choice (percentage of responses in the food hole) during manipulation of the unit dose of intravenous (IV) oxycodone ($n=11$). Under baseline conditions (marked "B" on the abscissa), the unit dose was 50 $\mu\text{g/kg/inj}$. Panel **B:** Food and drug intake during the unit dose manipulation. **C:** Choice during testing with subcutaneous (SC) naltrexone pretreatment ($n=13$). **D:** Intake during testing with naltrexone pretreatment. **E:** Choice during testing with intraperitoneal (IP) pretreatment with oxycodone ($n=15$).

Inset: Latency to first response of the session as a function of the pretreatment dose of naltrexone ("SC Nalt"), oxycodone ("IP Oxy") or vehicle ("V"). **F:** Food and drug intake during testing with IP oxycodone pretreatment over the whole session (black squares and black diamonds) and during only the portion of the session after the first response ("Adjusted"; gray upward and downward triangles). Adjusted values indicate the number of reinforcers that would occur if the intake rate during the period between the first response and the end of the session were to be maintained for two hours. * difference within curve. # difference between food hole and drug hole at same dose. [Details for within-curve differences marked by * are as follows. Panel A: Vehicle ("IV Veh") vs. all other points. Panel B, drug hole: 100 vs. all points except vehicle, 200 vs. all points except vehicle, and vehicle vs. all points except 100 and 200. Panel B, food hole: Vehicle vs. 25 and 50. Panels C and D: differs from vehicle. Inset: 4 mg/kg oxycodone vs. all other oxycodone points and vehicle. Panel F: differs from vehicle ("IP Veh").]

Table 1

Outline of experimental procedures. Phases (underlined) and schedules within phases were conducted in the order shown, except in the "Delay curves with fixed timeout" and "Timeout curves with fixed delay" phases, where the schedules were tested in mixed order across rats. Brackets indicate the paired delay and timeout values for each step in the initial delay curve determination. Values separated by "-" indicate range. "—" indicates not applicable.

PHASE and SCHEDULE	FOOD DELAY (seconds)	TIMEOUT DURATION (seconds)
<u>Pre-choice single-reinforcer training</u>		
Food only (with side reversals), then drug only or Drug only, then food only (without side reversals)	5 5	20 20
<u>Delay curves with delay and timeout increasing in steps</u> Food-drug choice	$\left(\begin{array}{c} 5 \\ 15 \\ 30 \\ 60 \\ 120 \end{array} \right)$	$\left(\begin{array}{c} 20 \\ 20 \\ 45 \\ 75 \\ 150 \end{array} \right)$
<u>Post-choice single-reinforcer testing</u>		
Food only Drug only	120 —	150 150
<u>Delay curves with fixed timeout</u>		
Food-drug choice Food only	5-120 5-120	150 150
<u>Timeout curves with fixed delay</u>		
Food-drug choice Food only Drug only	5 5 —	20-150 20-150 20-150
<u>Unit dose and pretreatment manipulations</u>		
Food-drug choice	120	150