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ORIGINAL INVESTIGATION

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Effects of morphine and naltrexone on impulsive decision making in rats

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Abstract *Rationale:* It has been reported that human opiate addicts discount delayed rewards more than non-addicts, indicating that they are more impulsive. However, it is not clear whether this difference reflects pre-existing traits, or the effects of exposure to the opiates. *Objectives:* This study was designed to investigate the effects of an opioid agonist and antagonist on delay discounting in rats. The study had three objectives: to determine (1) the acute effects of the opioid agonist morphine (MOR) on delay discounting, (2) the acute effects of the opioid antagonist naltrexone (NAL) on delay discounting, and (3) whether NAL reverses the effects of MOR on delay discounting. *Methods:* An adjusting amount procedure (AdjAmt) was used to determine how much animals discounted the value of delayed rewards. Acute doses of MOR (0.3, 1.0, and 1.8 mg/kg SC), NAL (0.01, 0.1, 1.0, and 10 mg/kg SC) and NAL (0.1 mg/kg SC) prior to MOR (1.8 mg/kg SC) were tested in 15 rats. *Results:* MOR dose dependently increased the rate of delay discounting (i.e., made the animals more impulsive). NAL alone had no effect on the value of delayed rewards, but NAL blocked the effects of MOR. *Conclusions:* These results suggested that the direct effects of MOR may contribute to the high level of impulsive behavior seen among opiate users.

Keywords Impulsivity · Delay discounting · Opiates · Choice · Operant · Conditioning

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Introduction

Impulsive behavior is often characterized as being socially inappropriate or maladaptive, and as being emitted quickly and without forethought (Oas 1985). This definition suggests that individuals who frequently engage in impulsive behaviors may fail to evaluate the consequences of their behavior appropriately. This emphasis on consequences is reflected in a widely used operational definition of impulsivity as being a preference for smaller, more immediate rewards over larger, more delayed rewards (Rachlin and Green 1972; Ainslie 1975; Herrnstein 1981; Logue 1988; Rachlin 1989; Richards et al. 1999a, 1999b). This operational definition is based on the observation that organisms "discount" the value of delayed consequences, such that the value of delayed rewards or punishments is inversely related to the delay of their occurrence. The discounting hypothesis of impulsivity suggests that the degree to which individuals discount delayed rewards is a measure of impulsivity. Thus, drugs or other manipulations that increase the rate at which rats discount the value of delayed rewards may be said to make the organism more impulsive. In the studies reported in this paper, we tested the effects of acute doses of morphine (MOR) and naltrexone (NAL) alone and in combination on discounting of delayed rewards in order to better understand the role of the opioid system on impulsive behavior.

Human drug users exhibit higher levels of impulsive behavior, as measured by delay discounting procedures. For example, human opiate addicts discount delayed monetary rewards more than non-addicts (Madden et al. 1997, 1999; Kirby et al. 1999; Odum et al. 2000; Giordano et al. 2002). Furthermore, even within groups of addicts, opiate users who also engage in other risky behaviors, such as needle sharing, discount delayed monetary rewards more than addicts who do not share needles (Odum et al. 2000). Although these studies indicate that opiate addiction is associated with high rates of delay discounting, they do not reveal whether this is due to exposure to the drug or to a pre-existing trait.

However, a recent study provided indirect evidence that opiates might have direct effects on impulsive behavior: Giordano et al. reported that mild opiate deprivation in opiate addicts increased discounting of delayed rewards (Giordano et al. 2002). This raises the possibility that opiates might directly alter delay discounting. Both humans and non-human animals discount the value of delayed rewards in a similar fashion, indicating that there may be a correspondence in the processes underlying delay discounting in humans and non-human animals. Therefore, in this study, we investigated the acute effects of MOR and NAL on discounting the value of delayed rewards in rats.

MOR is an opioid agonist that activates G_i protein-coupled mu-opioid receptors. The net effect of activating this receptor is to inhibit adenylyl cyclase activity and decrease cAMP levels (Uhl et al. 1994),which results in an overall decrease of neuronal activity. MOR produces a variety of behavioral and physiological effects in rats, including analgesia (Powell et al. 2002), both increases and decreases in locomotor activity (Vasko and Domino 1978; Iwamoto 1984; Kuzmin et al. 2000), and decreases in certain operant behaviors, such as lever pressing in order to gain access to wheel running and lever pressing for food (Molinengo 1964; McMillan 1973; Silva and Heyman 2001).

NAL is a non-specific opioid receptor antagonist which blocks most of the effects of MOR, at doses that produce little or no direct behavioral effects. Low doses of NAL block the analgesic and anxiolytic effects of MOR and reverse the constipating effects of MOR. At low doses NAL and other opioid antagonists produce few behavioral effects (Martin 1967; McMillan 1973), although at higher doses (e.g. 5.0 mg/kg and 10.0 mg/kg) NAL decreases locomotor activity and impairs operant responding in rats and mice (Castellano and Puglisi-Allegra 1982; Koek and Slangen 1984; White and Holtzman 2001). Opioid antagonists have also been shown to decrease deprivation-induced drinking (Brown and Holtzman 1979; Brown et al. 1980).

The present study examined the effects of MOR and NAL on impulsive behavior using an adjusting amount procedure (AdjAmt), which measures the value of the delayed rewards (Richards et al. 1997). This procedure is sensitive to the acute effects of drugs and neurochemical manipulations in rats, and it is similar to adjusting procedures used to measure discounting in humans (Rachlin et al. 1991; Richards et al. 1999b). Rats are given a choice between a standard alternative (a delayed constant volume) and an immediate adjusting amount of sucrose solution (adjusting alternative). The value of the adjusting alternative is increased after a choice of the standard alternative and decreased following a choice of the adjusting alternative. When the rat chooses the standard alternative and the adjusting alternative with equal frequency, we infer that the subjective value of the amount of sucrose solution on the adjusted alternative matches the subjective value of the standard alternative. This point is referred to as the indifference point. A decrease in the indifference point indicates that the animal values the delayed reward less and is thought to indicate increased impulsivity. The procedure is sensitive to the effects of acute drug administration. For example, D-amphetamine and methamphetamine decrease discounting, and the dopamine (DA) antagonists flupenthixol and raclopride increase discounting (Richards et al. 1999a; Wade et al. 2000).

As noted above, the difference in discounting between human opiate users and non-users could be due to preexisting differences in the individuals, or to effects of the drug. If they are due to effects of the drug, they could be due to the direct pharmacological effects, to effects of withdrawal of the drug (possibly opposite to the direct effects), or to lasting neural changes resulting from chronic exposure to the opiates. We examined one of these possible determinants, the direct effects of opiates, in animals with limited prior exposure to the drug. We first assessed the acute effects of several doses of NAL and MOR on delay discounting. Then, to verify that these effects were mediated by opioid receptors we attempted to block the effects of MOR with NAL.

Materials and methods

Subjects

Fifteen male Sprague-Dawley rats (Holtzman), weighing 540–720 g at the time of testing were used. The rats were housed in pairs and kept on a 12-h/12-h light/dark cycle with lights on at 0700 hours. The animals were water deprived for 23 h on testing days (Monday through Friday), with 20 min of free access to water at the conclusion of their testing sessions. Food was available ad libitum. On non-testing days (weekends), rats had both water and food available ad libitum. This study was conducted in accordance with the guidelines set up by the Institutional Animal Care and Use Committee of The University at Buffalo, The State University of New York.

Apparatus

Fifteen locally constructed experimental chambers were used (Richards et al. 1997). The chambers had aluminum front and back panels, plexiglas sides and top, and stainless-steel grid floors. The aluminum test panel had two feeder holes located on either side of a central snout poke hole. Stimulus lights were located just above both feeders and the center snout poke hole. The center snout poke hole and both feeders were monitored with infrared photo-sensors. A Sonalert tone generator with a frequency of 2900 Hz was mounted above and just left of the left stimulus light. Sucrose solution was presented to the rats in the feeder holes via syringe pumps (MED Associates, PHN-100) that pushed 60-ml syringes (Beckton Dickinson and Company). The entire apparatus was computer controlled through a MED Associates interface with MED-PC (version 4). The temporal resolution of the system was 0.01 s.

Procedure

The adjusting amount procedure is described in detail in Richards et al. (1997). Each experimental session ended after 40 min or the completion of 60 choice trials, whichever came first. Sessions also had a variable number of forced trials. Between trials there was a

15-s inter-trial interval (ITI). During this time, all the stimuli in the chamber were turned off. The activation of the stimulus light above the center snout poke hole signaled the beginning of each trial. The rat's first snout poke to the center hole initialized the trial and turned off the center stimulus light. Upon initialization of the trial the stimulus lights above the left and right feeders were turned on. The rat was then required to choose either the left or right sucrose solution dispenser. A snout poke into the left dispenser (standard alternative) resulted in the delayed (4 s) delivery of 150 μl of 3% sucrose solution. Choice of the right dispenser (adjusting alternative) resulted in the immediate delivery of an adjustable amount of 3% sucrose solution.

When the rat chose the left dispenser (delayed standard alternative), the stimulus light above the right dispenser turned off, and both the tone and the stimulus light above the left dispenser stayed on during the 4-s delay to reward period. Upon completion of the delay, the 150 μl of sucrose solution was delivered and both the tone and the stimulus light were turned off. An ITI of 11 s followed delivery of the delayed reward. During the ITI, the chamber was completely dark. At the end of the ITI, the stimulus light above the center snout poke hole was turned on to signal the start of the next trial. This 11-s ITI in addition to the 4-s delay comprised the 15-s time between response to one trial and the initiation of the following trial. If the rat chose the immediate reward side (the right dispenser) the light over the left dispenser was turned off and the rat immediately received an adjustable amount of sucrose solution. During the session, the amount of sucrose solution available on the adjusting side was dependent on the rat's choice in the previous trial. If the rat chose the immediate adjusting side, the amount of solution available on that side during the next trial decreased by 15%. If the rat chose the left delayed side, the amount of solution available on the adjusting side for the next trial increased by 15%. An ITI of 15 s followed delivery of the immediate adjusting reward. During the ITI, the chamber was completely dark. At the end of the ITI, the stimulus light above the center snout poke hole was turned on to signal the start of the next trial.

Forced trials occurred whenever the rat chose the same side in two consecutive trials. This was done to insure that the rat continually had experience with the consequences of choosing both sides. During a forced trial only the stimulus light above the side previously ignored was illuminated and the rat's only option was to choose that side. A typical test session contained approximately 20 forced trials. Forced trials were not used for data analysis, or for calculating the total 60 trials needed to end a session before the 40-min limit had expired.

The median amount of sucrose solution available for choosing the adjusting alternative was used to determine the indifference point. Rats usually reached a stable indifference point after approximately 30 trials. Therefore, only data from trials after the 30th trial were used for analysis. In the event that a rat performed fewer than 60 trials, only the trials beyond trial 30 were used; however, rats had to have completed a total of at least 40 trials for their data to be used.

In addition to the indifference point, data were also collected indicating the number of trials completed, the time it took the rat to respond to the center stimulus light (trial initiation latency), the time it took the rat to choose a side after the trial had been initiated (choice reaction time) and the percentage choice of the immediate adjusting alternative for trials after trial 30.

Initial training

The ITI was set at 5 s for the first 2 days of training and then at 10 s for the next 2 days. The amount of 3% sucrose solution available for choosing both the left (standard) and right (adjusting alternative) was set at 150 μl (with no delay) at the beginning of the session. The rats learned to make the center snout poke response and choose between the left and right sucrose solution dispensers in 2–5 days. The ITI was then set to 15 s (the final ITI) and the rats were trained further with 150 μl of sucrose solution on the standard side and delays of 0,1,2,4, and 8 s for 2 weeks, followed by 11 more weeks with 3% sucrose concentration and a 4-s delay. These conditions then remained constant for the duration of testing. The initial drop size for the adjusting alternative side for each drug condition was determined by averaging the indifference points from the week previous to the drugs administration.

Drug administration

MOR sulfate (Sigma Chemical, St. Louis, MO; S, 0.3, 1.0, 1.8 mg/kg) and NAL (Sigma Chemical, St. Louis, MO; S, 0.01, 0.1, 1.0, 10 mg/kg) were dissolved in saline (SAL) to form a solution of 1 ml/kg. The doses for all drugs were calculated as salts. During the NAL and MOR dose–responses drugs were injected subcutaneously on Tuesdays and Fridays, 20 min prior to the testing session. The sequence of doses of NAL for each rat was determined using a Latin-square design. Doses of MOR were given in ascending order. Each rat received each dose twice. The NAL dose–response was done before the MOR dose–response. NAL testing took place over a 7-week period. MOR testing began a week after NAL testing and lasted for 5 weeks. A week after the MOR dose–response determination MOR and NAL were co-administered in order to determine whether NAL would block the effects of MOR on the delay discounting task. During the co-administration part of the experiment the NAL (0.1 mg/kg SC) was given 40 min prior to the start of the session and MOR (1.8 mg/kg SC) was given 20 min before the start of the session. The treatment conditions during the co-administration study were SAL/SAL, NAL/SAL, SAL/MOR and NAL/MOR. Each combination was given twice. The co-administration study lasted 5 weeks.

Data analysis

All data used were calculated by averaging the two sessions the animals received each drug condition. The indifference points, number of trials, percent choice of the immediate adjusting alternative during trials after trial 30, choice reaction times and trial initiation latencies were analyzed using a one-factor within-subject analysis of variance (ANOVA) with repeated measures across the drug doses. If the ANOVA was significant, post-hoc *t*-tests were performed, comparing each of the drug doses to SAL. Similarly for the co-administration part of the study, paired-sample *t*-tests were used to compare the different drug conditions to the SAL/SAL condition, and the SAL/MOR condition was compared with the NAL/MOR condition. The Bonferroni method was also used to determine the required α-level for all analyses, with the overall α-level being 0.05.

Results

NAL effects

NAL (1.0 mg/kg and 10 mg/kg) had no effect on indifference points, but it increased both choice times and trial initiation latencies, and decreased the number of trials completed. This pattern is consistent with a non-specific impairment in performance. Indifference points during the last 30 trials of the session were similar after SAL and 10 mg/kg NAL (Fig. 1, top right), and none of the doses of NAL changed the mean indifference points (Fig. 1, top left). However, NAL (1 mg/kg and 10 mg/kg) increased choice reaction times ($F_{4,52}$=8.802, P<0.001; Fig. 1, bottom right), increased the latency to initiate trials ($F_{4,52}$=5.428, P<0.001; Fig. 1, bottom left) and decreased

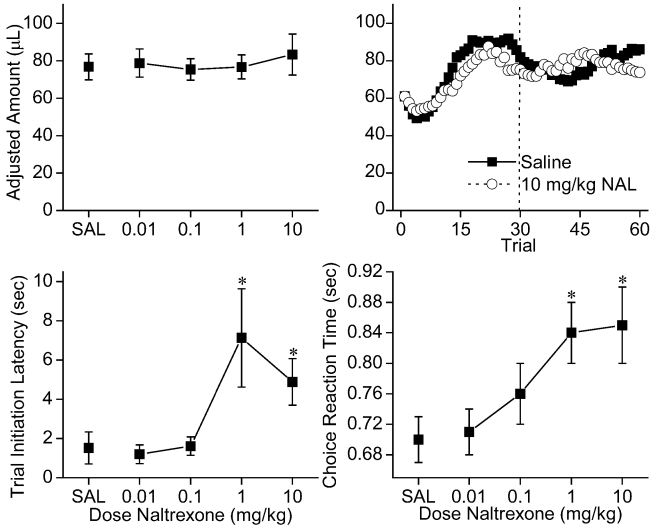

Fig. 1 The effects of naltrexone (NAL) on delay discounting. The *top left* plot shows that there was no effect of NAL on how much the rats valued the delayed large reinforcer. The points in this plot represent the mean and SEM of the amount of water available for choosing the adjusting immediate alternative during the last 30 trials of the session. The *top right* plot demonstrates how the rats adjusted the immediate amount of across the 60 trial session when given saline and the 10-mg/kg dose of NAL. The *bottom left* plot shows that NAL increased the latency to initiate trials and the *bottom right* plot shows that NAL also increased the latency to make a choice between the immediate and delayed alternatives. The *points* in the two *bottom* plots represent the mean and SEM of the of the initiation and choice reaction times, respectively. *Asterisks* indicate a significant difference from saline. See text for details

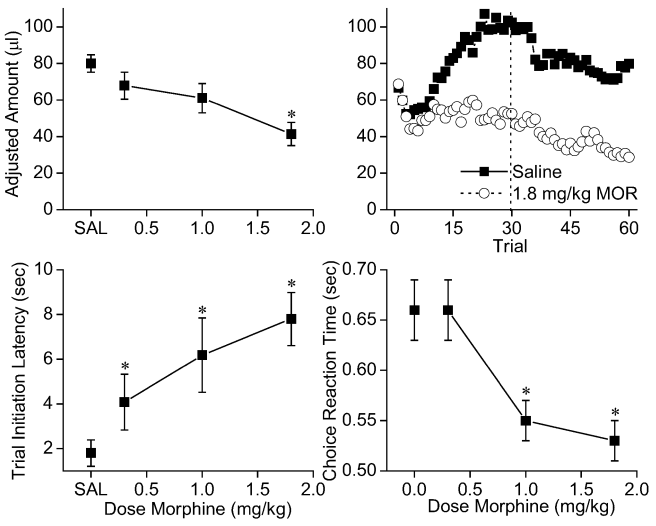

Fig. 2 The effects of morphine (MOR) on delay discounting. The *top left* plot shows that the rats adjusted the immediate amount of water to smaller amounts as the dose of MOR was increased. The points in this plot represent the mean and SEM of the amount of water available for choosing the adjusting immediate alternative during the last 30 trials of the session. The *top right* plot demonstrates how the rats adjusted the immediate amount of across the 60 trial session when given saline and the 1.8-mg/kg dose of MOR. The *bottom left* plot shows that MOR increased the latency to initiate trials, while the *bottom right* plot shows that MOR decreased the latency to make a choice between the immediate and delayed alternatives. The *points* in the two *bottom* plots represent the mean and SEM of the of the initiation and choice reaction times, respectively. *Asterisks* indicate a significant difference from saline. See text for details

Table 1 The effects of naltrexone on the number of trials completed (trials) and percentage choice of the adjusting immediate alternative during the last 30 trials (% adjusting side)

Dose naltrexone (mg/kg)				
Saline	0.01	0.1	1.0	10.0
Trials				
58.9±0.68	59.5±0.36	48.2±1.01	54.2±1.18	53.4±1.49
% Adjusting side				
46.5±0.80	46.2±1.24	48.9±1.32	48.6±1.87	46.7±2.1

Table 2 The effects of morphine on the number of trials completed (trials) and percentage choice of the adjusting immediate alternative during the last 30 trials (% adjusting side)

Dose morphine (mg/kg)			
Saline	0.3	1.0	1.8
Trials			
59.2±0.50	58.3±0.87	56.7±1.48	56.4±1.04
% Adjusting side			
48.5±1.11	48.7±1.71	44.9±1.30	52.4±2.43

the number of trials completed ($F_{4,52}$=10.973, P<0.001) (Table 1).

MOR effects

MOR decreased indifference points (i.e., made the animals more impulsive), although it increased the time it took the animals to initiate a trial and decreased the time it took the animals to make a choice between the delayed and immediate alternatives. The highest dose of MOR (1.8 mg/kg) significantly decreased indifference points ($F_{3,36}$=10.759, P<0.001; Fig. 2, top left). MOR (1.0 mg/kg and 1.8 mg/kg) decreased the animals' latency to choose between the delayed and immediate alternatives ($F_{3,36}$= 17.022, P<0.001; Fig. 2, bottom right) but at the same time it increased the latency to initiate trials (0.3, 1.0 and 1.8 greater than SAL; $F_{3,36}$=11.871, P<0.001; Fig. 2, bottom left). All three doses of MOR decreased the number of trials completed ($F_{3,36}$=8.962, P<0.001; Table 2).

NAL/MOR co-administration effects

NAL reversed the effects of MOR on indifference points and choice times, but not on trial initiation latencies. When NAL was co-administered with MOR the indiffer-

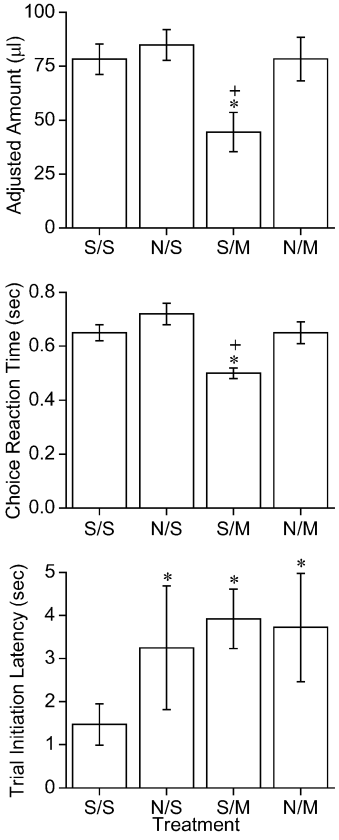

Fig. 3 The *plots* in this figure indicate the effects of co-administration of saline (SAL)/SAL, naltrexone (NAL)/SAL, SAL/morphine (MOR), and NAL/MOR on how much the rats valued the delayed rewards (*top*), choice reaction times (*middle*) and how long it took the rats to initiate trials (*bottom*). The *top plot* shows that a 1.8-mg/kg dose of MOR decreased the value of delayed reward and that 0.1 mg/kg NAL blocked this effect. The *middle plot* shows that a 1.8-mg/kg dose of MOR decreased choice reaction time and that 0.1 mg/kg NAL blocked this effect. The *bottom plot* shows that a 1.8-mg/kg dose of MOR increased the latency to initiate trials and that 0.1 mg/kg NAL did not block this effect. In all three plots, the *histogram bars* indicate the mean and SEM. *Asterisks* indicate a significant difference from SAL/SAL; *plus signs* indicate a significant difference from NAL/MOR. See text for details

Table 3 The effects of the co-administration of saline (SAL)/SAL, naltrexone (NAL)/SAL, SAL/morphine (MOR), and NAL/MOR on the number of trials completed (trials) and percentage choice of the adjusting immediate alternative during the last 30 trials (% adjusting side)

Treatment group			
SAL/SAL	NAL/SAL	SAL/MOR	NAL/MOR
Trials			
60.0±0.00	59.2±0.58	58.7±0.86	59.6±0.38
% Adjusting side			
46.0±2.16	46.3±2.18	46.2±1.89	49.0±1.88

ence points were not different from SAL controls (Fig. 3, top). Whereas, as noted above, choice reaction times were significantly longer after MOR (1.8 mg/kg) than SAL; this effect was blocked when animals were pretreated with NAL (0.1 mg/kg; Fig. 3, middle). NAL did not reverse the effects of MOR on trial initiation (Fig. 3, bottom), nor did it change the number of trials completed (Table 3).

Discussion

The primary finding of this study was that MOR decreased the indifference points, indicating that it made the rats more impulsive. This effect was dose dependent and was reversed by co-administration of the opioid antagonist NAL, which had no effect on the indifference points when administered alone. This finding is consistent with findings in human addicts, showing that opiate addicts are more impulsive than non-addicts (Madden et al. 1997, 1999; Kirby et al. 1999; Odum et al. 2000; Giordano et al. 2002). Interestingly, MOR increased the speed with which the rats chose between the immediate and delayed alternatives while at the same time slowing the speed with which the rats initiated trials. This may indicate that MOR reduced motivation to perform the operant behavior, but that once the task began the rats spent less time making their decision (acted more impulsively).

In contrast, NAL slowed both choice and trial initiation reaction times, perhaps indicating a lack of motivation due to suppressive effects on thirst/drinking, but also possibly indicative of a non-specific performance impairment. Both NAL and MOR dose dependently decreased the number of trials completed, indicating that both drugs were pharmacologically active.

The finding that MOR decreased indifference points suggests that it increased impulsivity. The increase in impulsivity is consistent with the apparently greater discounting observed in human populations who are thought to be impulsive, including opiate addicts. However, several alternative explanations of the present results should be considered. For example, previous studies with humans have shown that delay discounting also changes when the magnitude of the reinforcer changes (Green et al. 1997; Johnson and Bickel 2002). Therefore, in the present study, it is possible that MOR changed the indifference points because it decreased the value of the reinforcer. There is little evidence to support this idea, however, as MOR is generally thought to increase, rather than decrease, the reward value of food, especially palatable food (Berridge 1996). In addition, data from animal studies have generally failed to show an effect of reward magnitude in animals (Richards et al. 1997; Grace 1999).

Another alternative explanation is that MOR altered the perception of time, so that the delay to reward seemed longer. However, recent findings on the effects of MOR on time perception indicate that the drug does not affect

estimates of elapsed time (Odum and Schaal 2000). A third alternative explanation is that MOR may impair working memory. Hinson and colleagues (2003) recently reported that humans discounted delayed rewards more when working memory capacity was impaired by increasing working memory load (Hinson et al. 2003), and studies with rats suggest that MOR impairs working memory (Itoh et al. 1994; Pan 1998). Interestingly, this interpretation is consistent with findings with other drugs, such as DA antagonists, which both impair working memory (Sawaguchi and Goldman-Rakic 1991, 1994; Sawaguchi 2000) and increase delay discounting (Wade et al. 2000). Similarly in humans, alcohol impairs memory (Finn et al. 1999; De Oliveira and Nakamura-Palacios 2003) and, at least in one study, increased delay discounting (Richards et al. 1999b; Petry 2001). These results suggest that there may be a relationship between discounting of delayed rewards and memory.

In the present study, MOR clearly increased the speed with which rats chose between the delayed and immediate alternatives. What we refer to as "choice time" is the period of time during which the rat chooses between the standard and the adjusting alternative, and does not include the time taken by the rat to make the center snout poke that initiates the trial. Like other choice reaction times, the processes that occur during this choice period can be broken up into several components. Luce (1986) describes this process as: (1) the time it takes the physical signal (the offset of the center light and the onset of the lights above the two choice alternatives) to be perceived and processed into neuronal information, (2) the time it takes for a decision to be made, and (3) the time it takes for the completion of the motor response. The observation that MOR slowed trial initiation latencies suggests that it did not have a speeding up effect on component 1 (perception of stimulus) or on component 3 (motor output). Thus, the effect of MOR on decreasing choice reaction times is most likely caused by a decrease in the decision time (step 2 above). This is consistent with the characterization of impulsive behavior as being emitted quickly without forethought (Oas 1985).

The present findings have implications for the interpretation of other studies involving drugs that increase DA. The psychomotor stimulants D-amphetamine and methamphetamine, which are known to increase synaptic levels of DA, increase the value of delayed rewards (Richards et al. 1999b; Cardinal et al. 2000; Wade et al. 2000), although Evenden and Ryan (1996) have reported that AMPH had the opposite effect. In a subsequent study, Cardinal et al. (2000) found that the opposite effects of AMPH in the Evenden and Ryan study may have occurred because they did not include a cue that acted as a conditioned reinforcer during the delay to reward interval. It has been suggested that the effects of psychomotor stimulants on delay discounting may be mediated by increased DA in the nucleus accumbens (Cardinal et al. 2000; Wade et al. 2000). However, we found that MOR, which also causes substantial increases of DA levels in the nucleus accumbens (Di Chiara and Imperato 1988; Rada et al. 1991; Wise et al. 1995) decreased the value of delayed rewards. Thus, increases in DA levels are not simply related to decreases in impulsive behavior.

It is notable that the doses of MOR that increased delay discounting in the present study were low (under 2.0 mg/kg), relative to other studies of the behavioral effects of MOR that typically use doses up to and including 10 mg/kg. An interesting aspect of this study is the fact that low doses of MOR had such profound effects. The dose–response curve was originally planned for 2.5, 5, and 10 mg/kg, which would follow more closely with doses normally used for analgesia. However, the administration of the initial 2.5-mg/kg dose completely disrupted over three-quarters of the rats on the task. Also it should be noted that no signs of tolerance were observed during the duration of the experiments.

The results of this study suggest that opiate addicts may have particular difficulty during attempts to quit their drug use because the drugs themselves may bias the decision making about delayed consequences toward impulsive choices. For a drug user, most of the benefits of not using a drug are delayed. Thus, if opiates specifically affect the ability to choose delayed, over immediate, rewards, it can be seen that opiate addicts would have special difficulty in quitting. In this study acute administration of MOR substantially decreased the value of delayed consequences in rats. A parallel decrease in the value of delayed consequences after opiate self-administration in humans would impair the addict's ability to stop taking drugs.

Finally, it should be noted that there are several important differences between how delay discounting is measured in human and non-human animals, which need to be considered when generalizing from animal discounting experiments to humans. First, there are large differences in the length of delays to reward that are tested. Human studies use delays from hours to years, while animal studies generally use delays under 60 s. Second, studies with humans typically use hypothetical generalized conditioned reinforcers, such as money, while animal studies use real primary reinforcers such as food and water. Given these differences, it is important to use caution when generalizing from animals to humans.

Future research is needed to determine whether the increase in impulsive behavior observed after MOR administration is a function of specific opioid receptor sub-types and whether this effect is mediated by effects on cognitive processes (i.e., working memory). In addition it is important to determine whether similar increases in impulsive behavior are observed after chronic self-administration of MOR, which would more closely resemble the pattern of administration seen in human opiate addicts, as well as the effects of opiate withdrawal. Answers to these questions will allow the development of more sophisticated models of opiate addiction, as well as treatments.

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