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ORIGINAL INVESTIGATION

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Effects of methamphetamine on the adjusting amount procedure, a model of impulsive behavior in rats

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Abstract *Rationale:* Moderate doses of *d*-amphetamine (given both acutely and chronically) have been shown to decrease impulsivity in children with attention deficit hyperactivity disorder (ADHD) and to improve attention and learning in normal adults. In contrast, chronic doses of methamphetamine (METH) in drug abusers have been associated with increased impulsivity, and impairments in learning and attention. *Objectives:* We report the effects of METH on an animal model of impulsive behavior. *Methods:* Rats were tested using the adjusting amount (AdjAmt) procedure in which the animals choose between a delayed fixed (large) amount of water and an immediate adjusting (small) amount of water. In the acute METH study, rats were given a single dose of 0.5, 1.0, 2.0, and 4.0 mg/kg METH or saline 30 min before testing. In the chronic METH study, we determined the effects of the 4.0 mg/kg dose of METH injected chronically 1 h *after* behavioral testing for 14 days. Thus the rats were tested using the AdjAmt procedure 22 h after injections of METH or saline. *Results:* After 0.5, 1.0 and 2.0 mg/kg METH, the rats valued the delayed large rewards more than after saline, indicating that the METH decreased impulsiveness. At the 4.0 mg/kg dose, the rats failed to respond. Rats treated repeatedly with the post-session large behaviorally disruptive dose of METH valued the delayed large rewards less than the saline-treated rats, indicating that this dosing regimen of METH increased impulsiveness. *Conclusions:* In these experiments, the rats became less impulsive after acute non-disruptive doses of pre-session METH, whereas they became more impulsive after receiving repeated post-session injections of a dose that was behaviorally disruptive when administered acutely.

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Introduction

Moderate doses of amphetamine have been shown to be effective in reducing impulsiveness and hyperactivity in children diagnosed with attention deficit hyperactivity disorder (ADHD) (Gillberg et al. 1997; Findling and Dogin 1998; Solanto 1998). In non-clinical populations moderate doses of amphetamine have been shown to have beneficial effects on sustained performance (Caldwell and Caldwell 1997; Ward et al. 1997), and to improve learning and memory (Rapoport et al. 1980; Soetens et al. 1995; Ward et al. 1997). In contrast, chronic use of large doses of amphetamine by drug abusers has been associated with adverse behavioral effects, including anxiety problems, mood swings, depression, feelings of paranoia, and panic attacks (Hall et al. 1996; Williamson et al. 1997), impairments in learning and memory (McKetin and Mattick 1997, 1998), and amphetamine-induced psychosis (Snyder et al. 1974). In animals, large chronic doses of amphetamine have been associated with neurotoxicity (Seiden and Sabol 1995). In this paper, we report the effects of the amphetamine analogue methamphetamine (METH) on an animal model of impulsive behavior. Impulsive behavior has been operationally defined as preference for smaller immediate rewards over larger more delayed rewards. The rationale behind this operational definition is that impulsive individuals do not value delayed consequences as much as non-impulsive individuals, and are therefore more likely to choose small immediate rewards (Richards et al. 1999). For example, drug abusers may demonstrate this kind of impulsive behavior when they choose the small but immediate rewards of taking a drug over the delayed but larger benefits of abstaining from drug abuse. This interpretation is supported by recent studies that have found that opioid dependent individuals (Madden et al. 1997), alcohol abusers (Vuchinich and Simpson 1998) and individuals

with histories of drug dependence (Allen et al. 1997) discount the value of delayed rewards more than healthy volunteers.

We have developed a laboratory animal testing procedure, called the adjusting amount (AdjAmt) procedure, which measures the value of delayed large rewards, (Richards et al. 1997). The AdjAmt procedure gives rats repeated choices between a small amount of water, delivered immediately, and a larger amount of water available after a short delay. The amount of water available for choosing the delayed alternative remains fixed, and the amount of immediate water is systematically varied in order to determine the amount of immediate water at which the rat is indifferent between the delayed fixed amount and the immediate amount. This procedure differs from other choice procedures, which measure preference in terms of percent choice because at the indifference point the rats choose both alternatives with equal frequency. The AdjAmt procedure measures how much the animal values the standard alternative rather than which alternative is preferred. For example, in the present study we found that on average, the value of 150 µl water delayed by 4 s was equivalent to 50 µl water presented immediately. Drugs which decrease the indifference point (adjusted amount) are said to increase impulsivity because this indicates that the rat values the delayed reward less. Conversely, drugs, which increase the indifference point are said to decrease impulsive choice behavior because this indicates that the rat values the delayed reward more.

From a drug abuse perspective, as well as a therapeutic perspective, understanding the effects of amphetamine on this behavior is of interest. As described above, there are beneficial effects of moderate doses of amphetamine on impulsivity and attention in children with ADHD and normal adults, but detrimental effects of *d*-amphetamine and methamphetamine among drug abusers. Since amphetamine is taken chronically by both ADHD children and drug abusers, the differences in the effects of amphetamine in these two groups is probably not due to frequency of use and may be better explained by the total amount of drug consumed. The dose of amphetamine that enhances performance in ADHD children and normal volunteers is 0.2–0.5 mg/kg (Findling and Dogin 1998), whereas drug abusers have been reported to regularly consume, 0.93 g amphetamine, 8 times/month for 4 years; on the average (Williamson et al. 1997) (for a 70 kg person this converts to a 13.2 mg/kg dose). A second difference between the reported beneficial and detrimental effects of amphetamine is that the beneficial effects in ADHD children and normal human volunteers are observed immediately after drug administration, whereas some of the reported detrimental effects occurred after the peak pharmacological effects of amphetamine had dissipated. For example, Hall (1996) reported that anxiety and depression occurred 1–2 days after drug use, and attention and memory impairments have been observed in METH abusers who were drug free at the time of testing (McKetin and Mattick 1997, 1998). The detrimental effects of METH that are observed after peak levels have dissipated are more likely to be withdrawal effects rather than direct effects of METH. Despite the obvious differences in the populations and the context in which the drug is taken, some of the differences in the behavioral effects of these stimulant drugs may be related to the differences in the total dose to which these individuals are exposed and the time relative to drug administration that the effects are observed.

In the first of the two studies reported in this paper, we determined the dose response function of the effects of METH on the AdjAmt procedure. We found that METH dose dependently decreased impulsivity. In the second study, we determined whether METH administered chronically increase impulsive behavior in the AdjAmt procedure, by administering the METH (4.0 mg/kg) shortly after testing every day for 14 days. For the chronic dosing study, we selected the highest dose tested in the acute study. Although this dose disrupted the animals' behavior when it was administered acutely, in the chronic study the dose was administered after the sessions to avoid this problem. We found that chronic administration of METH increased impulsivity. This chronic dosing regimen may model patterns of drug use among METH abusers.

Materials and methods

Subjects

Nineteen Holtzman Sprague-Dawley rats (Harlan Sprague Dawley Inc., Indianapolis, Ind., USA), weighing between 350 and 450 g at the time of testing were used. The rats were housed four per cage. Lights were on in the colony room from 7:00 a.m. to 7:00 p.m. Food (Teklad Laboratory Diet #8604, Harlan Sprague Dawley) was available without restriction. On the training days (Monday through Friday), the rats received 20-min access to water at the end of testing sessions. On non-training days (Saturday and Sunday), the rats were given 20-min access to water between 10:00 a.m. and 2:00 p.m.

Apparatus

Eight locally constructed experimental chambers were used. These chambers are described in detail by Richards et al. (1997). The chambers had stainless steel grid floors, aluminum front and back walls, Plexiglas sides and a Plexiglas top. The front wall of the chamber served as the test panel and had two water dispensers located on either side of a centrally located snout poke hole. Stimulus lights were mounted above the two water dispensers and the center snout poke hole. The water dispenser stimulus lights were arranged so that they were level with the rat's eyes when the rat's snout interrupted an infrared beam in the center snout poke hole. A Sonalert tone generator with a frequency of 4500 cps was mounted above the left stimulus light. Snout pokes and head entries into the water dispensers were monitored with infrared detectors. Each water dispenser was calibrated to provide a precisely measured amount of water. The precise amount of water was under the control of a computer program.

The eight chambers were connected to a 33 MHz 486DX microcomputer using a MED Associates interface (MED Associates Inc., St Albans, Vt., USA). The experimental contingencies were programmed using the MED-PC programming language. The temporal resolution of the system was 0.01 s.

Procedure

The AdjAmt procedure is fully described by Richards et al. (1997). Each session consisted of 60 discrete choice trials plus a variable number of forced trials. Each trial was separated by an inter-trial interval (ITI). The total time between the start of each trial was 30 s plus the time taken for the rat to make a choice response. During the ITI, all of the stimuli in the chamber were off. Turning on the light above the center snout poke hole signaled the start of each trial. The first response (snout poke) to the center hole after the beginning of a trial caused the stimulus light above the center hole to be turned off and the stimulus lights above the left and right water dispensers to be turned on. The rat was then required to choose between the left and right water dispensers. Inserting the head into the left dispenser always resulted in the delivery of 150 µl water after a 4-s delay. The adjusting amount of water was always presented on the right side. Inserting the head into this dispenser resulted in the immediate delivery of a variable amount of water.

When the animal chose the left delayed side, the light above the adjusting alternative was turned off and a tone turned on. This tone (and light above the delayed alternative) remained on throughout the 4-s delay period. At the end of the delay period a 150 µl drop of water was delivered and the tone and light were turned off for the remainder of the 30-s trial. Note that when the rat chose the delayed side the ITI duration was 30 s minus the 4-s delay (26 s). When the rat chose the immediate alternative the ITI duration was 30 s. When the animal chose the adjusting alternative, an amount of water was delivered immediately and the stimulus lights above the left and right water dispenser apertures turned off for the remainder of the 30 s. During each session, the amount of water available on the adjusting alternative was systematically varied. If the animal chose the standard, the amount delivered on the adjusting alternative was increased by 10% on the next trial. If the animal chose the adjusting alternative, the amount delivered on the adjusting alternative was decreased by 10% on the next trial.

Forced trials were used to insure that the rats were exposed to the consequences of choosing both the delayed 150 µl amount of water and the immediate adjusted amount of water from the adjusting alternative. Choice of either the delayed or the adjusting alternative on two consecutive trials was followed by a forced trial in which the rats were required to choose the opposite side. On forced trials, only the stimulus light above the required alternative was turned on after the central snout poke response. Responses to the non-illuminated side had no programmed effect.

Initial training

On day 1 of training the ITI was 10 s and the standard was 150 µl water presented immediately. The rats were trained in daily 1-h sessions under these conditions until they completed 60 trials within a 1-h period. The rats learned to make the center snout poke response and choose between the left and right water dispensers in 2–5 days. Then the ITI was set at 30 s and the regular experimental procedure implemented. No further shaping by the experimenter was required. After initial training, the rats trained on the AdjAmt procedure for 16 weeks before drug testing. During the first 12 weeks of training, the delay to the 150-ml amount remained constant during each daily session but changed in a random fashion so that a different delay was tested on each of the 5 training days in a week. The delays used were 0, 2, 4, 8, and 16 s. After 12 weeks of training with this procedure, discount functions similar to those we have previously reported were obtained (Richards et al. 1997). The rats then received 4 weeks of daily training with a constant 4-s delay to 150 µl water before drug testing was started. A delay of 4 s was chosen as the test standard because this delay produced a baseline from which both decreases and increases in the adjusted amount after drug administration could be observed. In an effort to increase baseline stability, the starting amount on the adjusting alternative for each rat was set to a value equal to its indifference point, based on data collected before drug administration was started. These individual starting amounts were maintained throughout the rest of the study.

Drug administration

D-Methamphetamine hydrochloride (METH) (Sigma, St Louis, Mo., USA) (V, 0.5, 1.0, 2.0, 4.0 mg/kg) was dissolved in saline to form a solution of 1 ml/kg. METH doses were calculated as salts. Doses of the drug were injected intraperitoneally.

In the acute dose response determination METH was injected on Tuesdays and Fridays 30 min before the testing. The sequence of doses for each rat was determined using a balanced Latin square sequence. Drug administration for the acute study took place over a 2-week period.

The chronic study began 1 week after the conclusion of the acute METH study. In the chronic study the rats received daily intraperitoneal injections of either a 4.0 mg/kg METH or saline, administered 1 h after each behavioral test session (i.e., approximately 22 h before the next session). The rats were given 20-min access to water immediately after test sessions. On weekends, the rats were not tested in the behavioral procedure, but received 20-min access to water in their home cage, and received the daily injections of METH injected 40 min after this. The 19 rats were divided into two groups of nine and ten rats, equated for performance on the AdjAmt task. One group (n=9) received daily injections of saline for 14 days followed by 14 days of daily METH injections. The other group (n=10) received daily injections of METH for 14 days followed by 14 days of daily saline injections. Each 14-day block started on a Monday and ended on a Sunday. After 4 weeks (28 days), all 19 rats in the chronic study had received 14 daily injections of both saline and METH in a counterbalanced order.

Data analysis

The median amount of water available on the adjusting alternative during the last 30 choice trials of each 60-trial session was used as the estimate of the indifference point (i.e., the value of the delayed reinforcer). Sometimes the rats failed to complete all 60 trials. In this case, the median drop size was calculated for those trials completed after the 30th trial. Only test sessions in which the rats completed at least 40 trials were included in the data set. Forced trials were not included in this calculation.

In addition to the indifference point measure, percent choices of the immediate adjusting alternative, response latencies, and choice latencies were collected. Response latency was the time it took a rat to make a snout poke response after the center stimulus light was turned on to signal trial onset. The choice latency was the time it took a rat to move from the center snout poke hole and choose either the standard or the adjusting alternative. These data were also taken from the last 30 trials of the session and the data from forced trials were not included.

In the acute dose-response determination study, the effects of the METH on the four dependent measures described above (indifference points, percent choices of the immediate alternative, response latencies and choice latencies) were analyzed using a one-factor within subject ANOVA with drug dose as the main effect. If the ANOVA was significant, Post-hoc paired t-tests were used to compare the doses of METH with saline treatment. A Bonferroni correction was used to control for overall error rate. The significance level was set at $P<0.05$.

In the chronic study, the same dependent measures described above for the acute study were used (indifference points, percent choices of the immediate alternative, response latencies and choice latencies). The test sessions of the saline treatment phase were combined and compared to the corresponding METH treatment sessions using a within-subject paired t-test.

Results

Acute study

Because at least 40 trials were needed to estimate indifference points, the data from rats that completed fewer

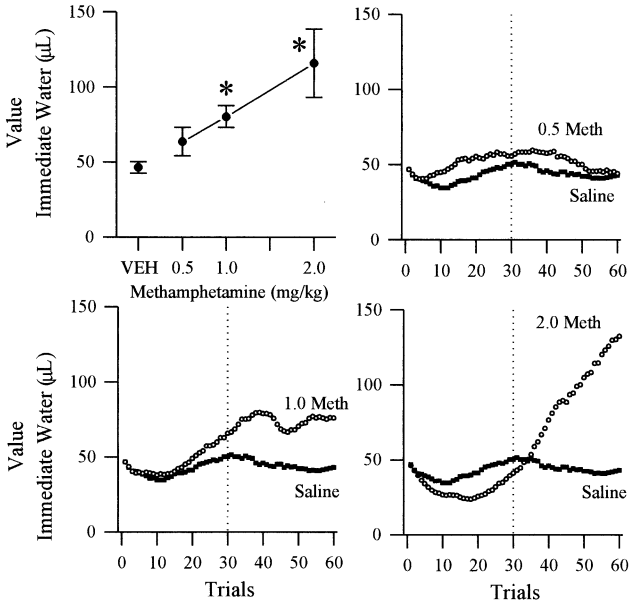

Fig. 1 The *top left plot* shows that the rats adjusted the immediate amount of water to larger amounts as the dose of METH was increased. The points in this plot represent the mean and SE of the amount of water available for choosing the adjusting immediate alternative during the last 30 trials of the session. The *other three plots* demonstrate how the rats adjusted the immediate amount across the 60-trial sessions when given saline and one of three doses of METH

than 40 trials could not be included in the analysis. Three rats failed to complete 40 trials at the 2.0 mg/kg dose and all of the rats failed to complete 40 trials at 4.0 mg/kg dose. Injection of METH 30 min before testing resulted in a dose-dependent increase in the indifference point (Fig. 1). It was found that indifference points were significantly increased by METH [$F(3,45)=5.473$, $P=0.003$]. Post-hoc *t*-tests showed that compared to vehicle both 1.0 mg/kg and 2.0 mg/kg METH significantly increased the indifference points.

Figure 1 shows the progression of adjusted values of the immediate amount of water across the 60 trials of the session. The figure shows that in the vehicle condition, the values reached a stable indifference point between trials 31 and 60. METH increased the value of the indifference point in a dose-dependent manner. After 0.5 mg/kg METH, animals tended to value the delayed amount more (see 0.5 METH plot). After the 1.0 mg/kg dose of METH, the rats reached a stable indifference point during the last 20 trials of the session, at a level higher than the vehicle level (shown by the flat portion of the 1.0 METH plot in Fig. 1). After the 2.0 mg/kg dose of METH, the animals failed to reach an indifference point, and continued to choose the delayed reward more frequently throughout the 60-trial session (shown by the monotonically increasing trend in Fig. 1).

The effects of acute METH on percent choices of the immediate adjusting alternative, response latencies and choice latencies are shown in Table 1. There was a significant effect of acute METH on the percent choices of

Table 1 Effects of acute moderate doses of METH on percent choices of the immediate adjusting reward alternative and measures of response speed during the last 30 trials. Values are means (±SEM; *$P<0.05$

Dose (mg/kg)%	Choice of immediate reward	Response latency (s)	Choice latency (s)
Saline	50.3±2.27	1.00±0.13	0.51±0.02
0.5	50.7±3.53	0.78±0.07	0.49±0.02
1.0	44.8±2.70	0.80±0.07	0.47±0.02
2.0	27.2±4.63 *	0.74±0.04	0.45±0.03

the immediate adjusting alternative [$F(3,45)=9.201$, $P<0.001$]. Table 1 indicates that after saline and 0.5 and 1.0 mg/kg METH, the rats chose the immediate side approximately 50% of the time during the last 30 trials of the session (indicating indifference), whereas post-hoc *t*-tests indicated that after 2.0 mg/kg METH the rats chose the immediate adjusting alternative significantly less. Table 1 also shows that although METH tended to decrease response and choice latencies, these effects were not significant.

Chronic study

The histogram in Fig. 2 shows the mean indifference points during the last 30 trials of the test sessions. Compared to saline, chronic METH significantly decreased indifference points [$t(18)=3.748$, $P=0.001$]. Figure 2 also shows the change in the animals' responses across the 60 trials of the test. Both the saline- and METH-treated animals reached stable indifference points. There were no significant differences between the groups on the percent of trials in which they chose the delayed alternative, and response or choice latencies (Table 2).

Discussion

Acute study

Rats were given four doses of METH (saline, 0.5, 1.0, 2.0, and 4.0 mg/kg) 30 min before testing with the AdjAmt procedure. A dose dependent increase in the amount of water at the indifference point was observed, indicating that the rats valued the delayed water more. At the 1.0 mg/kg dose of METH the rats demonstrated a clear increase in the indifference point during the last 30 trials of the test session, indicating that they valued the delayed alternative more at this dose of Amphetamine (Fig. 1). The 2.0 mg/kg dose of METH appeared to disrupt performance on the AdjAmt procedure. Examination of the trials plot for the 2.0 mg/kg dose indicates that during the first 30 trials the rats showed an increased tendency (compared to saline) to respond on the immediate adjusting alternative. During that the last 30 trials, the rats showed the opposite trend and continued to re-

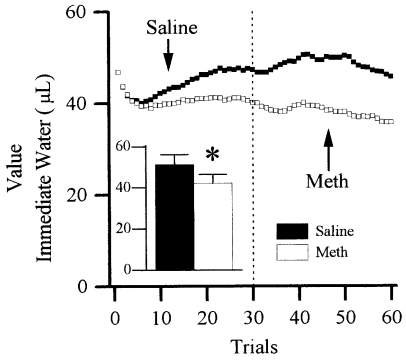

Fig. 2 Compared to the saline, chronic METH significantly decreased the indifference point. The *histogram* shows the means and SE of the amount of water on the immediate side during the last 30 trials of the session (indifference points). The *line plot* shows the adjusted amount of water across the 60-trial test session

Table 2 Effects of chronic large doses of METH on percent choice of the immediate adjusting reward alternative and measures of response speed during the last 30 trials. Values are means (±SEM; **P*<0.05

Dose (mg/kg)%	Choice of immediate reward	Response latency (s)	Choice latency (s)
Saline	48.9±1.11	0.89±0.08	0.50±0.02
4.0	49.0±0.98	1.17±0.20	0.53±0.02

spond on the delayed alternative despite the availability of increasing amounts of water on the immediate alternative. The significant decrease in the percent choice of the immediate adjusting alternative at the 2.0 mg/kg dose indicates that the rats did not reach an indifference point at this dose. The fact that three of the rats failed to respond at the 2.0 mg/kg dose provides further evidence that this dose of METH disrupted performance on the AdjAmt task. These results are consistent with interpretation that acute injection with1.0 mg/kg METH increased the value of the delayed reinforcer and decreased impulsive choice behavior.

These results are consistent with the clinical observation that moderate doses of amphetamine decrease impulsivity and improve sustained attention in humans (Caldwell and Caldwell 1997; Ward et al. 1997). However, the results are not consistent with other studies in laboratory animals, using different behavioral tasks, in which amphetamine increased impulsivity. In these studies, impulsivity was operationally defined in terms of preference for an immediate small reward over a delayed but larger reward (Charrier and Thiebot 1996; Evenden and Ryan 1996). However, the procedures used in these studies to measure impulsivity differed substantially from the present study. First, the AdjAmt task included a forced trial procedure which insured that the rats had recently sampled both alternatives, whereas the procedures used in the Charrier and Thiebot (1996) and Evenden and Ryan (1996) studies did not have forced trials. The forced trial procedure may reduce the likelihood of perseverative choices induced by amphetamine. Second, the AdjAmt procedure uses water as a reward while the Charrier and Thiebot (1996) and Evenden and Ryan (1996) studies used food rewards. The anorexic properties of amphetamine may result in differential effects on food and water motivated tasks. Third, the AdjAmt procedure was explicitly designed to be sensitive to the effects of acute manipulations. In a previous study, we (Richards et al. 1997) have demonstrated that the AdjAmt procedure is sensitive to day-to-day changes in delay (0–16 s) and the amount (100–200 µl) of water on the delayed side. The sensitivity of the AdjAmt procedure may be related to the fact that the amount of water available for choosing the immediate alternative is constantly changing (i.e., increasing or decreasing by 10% after every choice), requiring a certain flexibility from the animals to maintain a stable indifference point. This sensitivity to the changing contingencies within the sessions may make the animals more sensitive to the effects of amphetamine. In contrast, in the Charrier and Thiebot (1996) procedure the rats learned the difference between a fixed delayed large number of food pellets and a fixed more immediate small number of food pellets which remained constant within the session. A degree of flexibility was required in the Evenden and Ryan (1996) procedure, which required the rats to switch preference from the large reward to a small reward as the delay to the large reward was systematically increased during the session. Under these training conditions, the rats learned to choose the large reward at the beginning of the session and then switch to the small immediate reward as the delay to the large reward became longer. However, rats trained on this procedure demonstrated a decrease in preference for the large reward across the session even when there was no delay to the large reward (Evenden and Ryan 1996; Fig. 5) (although this decrease was not as great as when actual delays were presented). Finally, the measure of preference in the AdjAmt procedure is amount of immediate water on the adjusting alternative at the indifference point while the measure of preference in the Charrier and Thiebot (1996) and Evenden and Ryan (1996) studies is percent choice. Although these measures are conceptually the same, this difference may also account for the different results.

Other differences which may explain why the present results differ from those previous reported in the literature include: (a) that the response was a nose poke versus a lever press, (b) that it was possible for the animals to respond during the delay interval (although these responses had no programmed effect), (c) that the locations of the constant and adjusting water deliveries were spatially separated, (d) that the delay was 4 s rather then up to 60 s (Evenden and Ryan 1996), (e) that the fixed value was the delayed option (rather than the immediate option, as in the Evenden and Ryan (1996) study. For now, it cannot be determined which, if any, of these differences contributed to the results.

An important aspect of the AdjAmt procedure reported in Richards et al. (1997) is that it produces discount functions that are similar to those observed in humans. In both rats and humans, discounting of reward value by delay is well described by an hyperbolic function (Mazur 1987; Rachlin et al. 1991; Green et al. 1994; Kirby and Marakovic 1995). We have also found this hyperbolic pattern in a recent study with humans using a variation of the AdjAmt procedure used here (Richards et al. 1999). The similarities in discount functions between humans and rats trained on the AdjAmt procedure support the assumption that the procedures used across the two species represent the same basic underlying processes.

To summarize, the effects of acute METH on the AdjAmt procedure support the idea that amphetamine decreases impulsivity, consistent with the reported effects of moderate doses of amphetamine in both clinical and non-clinical populations (reviewed in introduction). This result extends our understanding of how amphetamine affects behavior, and supports the validity of the AdjAmt procedure as a good measure of impulsive behavior in animals.

Chronic study

In the chronic METH study it was found that the amount of water at the indifference point decreased after 2 weeks of treatment with daily doses of 4.0 mg/kg METH, indicating that the rats valued the delayed water less. This result suggests that chronic post-session injections of METH made the animals more impulsive. There are, however, other interpretations of the results. One interpretation of the decrease in the value of the delayed reward after chronic METH is that chronic injection of METH after the session may have led to an association between testing and subsequent METH induced malaise, thus devaluing the reinforcers available in the session. A number of studies have shown that injection of METH after consuming a novel tasting fluid results in conditioned taste aversion (Martin and Ellinwood 1973; Goudie et al. 1976; Parker 1995). However, the development of such an association seems unlikely in the present experiment because the taste of the water was not novel and the rats had a very long history of drinking water in the experimental apparatus in the absence of a drug injection. Furthermore, we have previously studied the effects of devaluing the reinforcers available during the session by manipulating the level of water restriction (Richards et al. 1997). We found that giving the rats 20-min access to water 4 h prior to the session (instead of the usual 23 h) resulted in slower choice and response latencies but did not change the indifference points. Our interpretation of these results (Richards et al. 1997) is that deprivation (and presumably any malaise associated with reforcers available during the session) affects the value of both the immediate and delayed reinforcers proportionally, so that there is no change in the relative values of the delayed and immediate reinforcers. In any case, the absence of a slowing of choice and response latencies indicates that devaluation of reinforcer value by association with subsequent drug induced malaise did not occur.

The finding that repeated administration of a relatively large dose of METH had an effect on impulsivity that was opposite to that of acute treatment is consistent with opposing patterns found in other paradigms. Chronic treatment with amphetamine has been shown to cause either sensitization or tolerance, depending on various factors including dose, frequency of administration, environmental and temporal context, and behavioral task (for reviews, see Robinson and Becker 1986; Robinson and Berridge 1993; Segal and Kuczenski 1994). In addition, removal of the drug after chronic treatment results in characteristic withdrawal symptoms, which are often opposite to the effects, observed during the acute drug state. For example, ICSS reward threshold is lowered by acute amphetamine treatment, but raised during withdrawal (Wise and Munn 1995). In the present study, the effects of METH on impulsive behavior 22 h after administration were opposite to the effects of acute doses of METH, suggesting that the day-after effects may be related to withdrawal. The procedure used in the present study does not allow us to separate an effect of withdrawal from the effects of chronic administration.

There is some evidence that intracellular concentration of dopamine 22 h after injection may have been decreased by the chronic injection regimen used in this study. Imperato et al. (1996) treated rats with 1.5 mg/kg amphetamine twice daily at 12-h intervals, for 14 days. They reported that basal dopamine release was decreased beginning on day 5 of the treatment period (measured immediately before the first daily amphetamine injection) and remained depressed for the subsequent 9 days of treatment. Also, Persico et al. (1995) measured postmortem tissue content of dopamine in the striatum and found that dopamine levels were diminished between 12 and 54 h after the last of a series of chronic amphetamine injections (7.5 mg/kg, twice daily for 14 days). Taken together, these studies indicate that the basal release of dopamine, and tissue content of dopamine 22 h after METH treatment, may be decreased. These findings are consistent with the observations of compensatory behavioral reversals seen during withdrawal. These results suggest that increased impulsiveness during withdrawal may be associated with diminished DA transmission. This suggestion is further supported by unpublished data from our laboratory indicating that the DA antagonists haloperidol, flupenthixol and raclopride increase impulsivity on the AdjAmt procedure. Further studies are needed to determine the relationship between the increases in impulsive choice, withdrawal and DA transmission.

The results of the experiments reported in this study indicate that METH can both increase and decrease impulsive behavior depending upon injection regimen. These differences in the effects of METH may be accounted for by any of three factors, or a combination

thereof: (1) differences in the effects of acute versus chronic METH administration, (2) dose size, and (3) the time since the last injection relative to testing. Which of these factors is critical could be addressed in parametric studies with the AdjAmt procedure. An important clinically relevant study would be to compare the effects of low dose chronic administration of METH (for example 1.0 mg/kg) with the effects of chronic administration of a larger dose of METH. Also, the crossover design of the present study did not allow for observation of how quickly chronic METH produced the changes observed in Fig. 2. Future studies should allow a "wash out" period between the end of METH treatment and the beginning of Saline treatment.

In summary, these studies indicate the effects of amphetamine in rats trained on the AdjAmt procedure may be similar to its effects in humans. Acute injections of METH were found to decrease impulsive behavior in the animal model, analogous to the effects of moderate doses of amphetamine in children with ADHD and normal human volunteers. In contrast, repeated injections of METH were found to increase impulsive behavior on the animal model, analogous to the higher likelihood of impulsive behavior that is associated with METH abuse. Greater impulsivity as measured by delay discounting has also been reported among other drug-using populations, including heroin users (Madden et al. 1997), alcohol abusers (Vuchinich and Simpson 1998), cigarette smokers (Mitchell 1998) and individuals with unspecified histories of drug dependence (Allen et al. 1997), compared to healthy volunteers. Although it is not possible to rule out pre-existing differences among these drug users compared to controls, these findings are consistent with the idea that chronic exposure to drugs increases impulsivity. Further studies are needed to investigate this suggestion more fully. Laboratory experiments in which impulsivity levels are measured in humans before and after chronic treatment with drugs of abuse such as METH cannot be done for ethical reasons. A valid animal model of impulsive behavior provides one way to address this problem.

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