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Effects of acute and chronic methylphenidate on delay discounting

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ABSTRACT

Methylphenidate (MPH) is one of the most common therapeutics used for the treatment of attention-deficit/hyperactivity disorder (ADHD), which consists of symptoms of inattention, and/or impulsivity and hyperactivity. Acute administration of MPH has been found to decrease impulsive choice in both humans and nonhuman animals, however, little is known about potential long-term changes in impulsive choice due to chronic administration of MPH. In the present experiment, effects of acute and chronic MPH (1.0–10.0 mg/kg) were assessed on impulsive choice in the adult male Spontaneously Hypertensive Rat (SHR) to determine the extent of behavioral changes after chronic MPH exposure. Subjects chose between an immediate single food pellet and three food pellets delivered after a delay that increased within session (0 to 16 s). At relatively higher doses during acute and chronic administration, choice maintained by the larger reinforcer was disrupted when there was no delay to either outcome, suggesting that MPH may be affecting stimulus control under the current delay-discounting task. When this disruption was not observed, however, MPH effects were selective in that only one intermediate dose (3.0 mg/kg) decreased mean impulsive choice at one delay (8 s) following acute administration. The same effect was observed following chronic MPH administration except that the dose was higher (5.6 mg/kg) and the delay was shorter (4 s). Chronic administration of MPH did not show any negative indicators (e.g., an increase in impulsive choice) when administration was discontinued.

1. Introduction

ADHD is a common neuropsychiatric illness with prevalence among children estimated between 5 and 9% (Dopheide and Pliszka, 2009). Of individuals diagnosed with ADHD in childhood, approximately 80% continue to exhibit problems into adolescence and 50% continue showing symptoms into adulthood. Core symptoms of the disorder consist of deficiencies related to inattention, and/or impulsivity and hyperactivity and can impede an individual's performance in academic and social environments (Barkley, 2002). Recent attention in clinical and preclinical research has focused on the assessment of impulsivity in ADHD-diagnosed individuals and nonhuman animal models to develop a better understanding of the behavioral and cognitive aspects of the disorder and provide therapeutic implications for pharmacological agents.

One common operational definition of impulsivity (referred to as impulsive choice) is choice for a smaller, more immediate reinforcer to the exclusion of a larger, more delayed reinforcer. The converse is referred to as a self-controlled choice (cf. Ainsle, 1974). When the delays to reinforcer presentation are relatively short, subjects generally choose the larger outcome. As the delay to presentation increases, however, choice may switch to favor the smaller, more immediate outcome. Individuals differ in when they make the switch from the larger option to the smaller one and this can be captured by delay-discounting functions (cf. Mazur, 1987). For example, it is the general case that individuals diagnosed with ADHD choose smaller-immediate rewards over larger-delayed rewards more than control participants, indicating greater impulsive choice (for a review see Luman et al., 2005, but also see Scheres et al., 2006 showing no difference in discounting).

In a study conducted by Barkley et al. (2001), ADHD-diagnosed individuals made more choices for smaller, immediate amounts of hypothetical money compared to a larger amount of hypothetical money across a range of hypothetical delays (1, 12, 60, and 120 months) relative to control subjects. The difference in discounting was only found when the larger amount was $100, but differences between groups were not evident at $1000 indicating that parameters of procedural variables may affect the outcome. As other studies have indicated baseline differences in choice between larger-delayed rewards and smaller-immediate rewards between ADHD-diagnosed individuals and control participants (Luman et al., 2005; but see Scheres et al., 2006), a next step would be to determine if ADHD therapeutics alters choice on a delay-discounting task.

The focus of the present study was to assess acute and repeated effects of methylphenidate (MPH; a first-line treatment for the symptoms of ADHD) in a discrete-trials delay-discounting task for nonhuman animals (Evenden and Ryan, 1996). One approach to

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better understand an effect of acute and chronic MPH on behavioral measures relevant to ADHD is to utilize animal models and methods that enable control over variables of interest that may not be possible with clinical populations. Presently, little is known about chronic effects of MPH on measures of impulsive choice in both humans and nonhuman animals.

In humans, acute administration of MPH was found to decrease impulsive choice in a delay-discounting task in ADHD-diagnosed individuals relative to a placebo condition only when the delays and rewards were experienced (Shiels et al., 2009). Interestingly, acute administration of MPH did not alter discounting when the delays and rewards were hypothetical. In nonhuman animals, acute administration of MPH has also been shown to decrease impulsive choice in Sprague–Dawley and Wistar rats (Pitts and McKinney, 2005; van Gaalen et al., 2006, respectively) in a discrete-trials delay-discounting procedure. Effects of acute and chronic MPH on impulsive choice in the present study were assessed in the Spontaneously Hypertensive Rat (SHR), a purported animal model of ADHD (cf. Sagvolden, 2000), using a discrete-trials choice procedure. One study has shown that acute MPH reduces impulsive behavior in juvenile Wistar rats, but not in adult Wistar, SHR, or Wistar Kyoto rats (Bizot et al., 2007), however, the procedure involved the use of a T-maze and only assessed drug effects across two delays (0 and 30 s) to the larger reinforcer. The extent to which procedural variables, such as different delays, affect impulsive choice is worthy of continued study as noted by the contrasting results found in the human research discussed above (e.g., Barkley et al., 2001; Shiels et al., 2009).

Since ADHD-diagnosed individuals treated with MPH receive it on a repeated basis, and the diagnosis and treatment of ADHD can extend from childhood into adulthood, it is critical to characterize the drug's long-term effects on relevant behavioral measures such as impulsive choice. The present study was designed to systematically replicate previous findings based on the acute effects of MPH in the SHR and extend the analysis of MPH's effect on choice by determining chronic and withdrawal effects. It was of primary interest to determine if tolerance (reduced effectiveness of MPH), sensitization (enhanced effectiveness of MPH) or sustained efficacy is evident after repeated exposure to MPH under a discrete-trials delay-discounting procedure and if there were any changes in choice after the cessation of chronic drug treatment.

2. Materials and methods

2.1. Subjects

Eight experimentally experienced male adult Spontaneously Hypertensive Rats (SHR) served as subjects. Each subject was briefly tested under the same delay-discounting task used in the current experiment, but the order of delay presentation was varied instead of presented in an ascending order. Each rat was approximately one year of age at the start of the drug administration procedure. They were housed individually in an approved facility on the West Virginia University campus. The colony was maintained at approximately 21–27 °C and a 12-hr reverse light–dark schedule was in effect. Food access was controlled at 12–15 g 1 h after each experimental session so that each animal was food-restricted for approximately 22 h before the start of each experimental session. Body weights increased during the course of experimentation commensurate with age and ranged from 230 to 400 g from start to finish of the experiment. Rats had free access to water in their home cages.

2.2. Apparatus

Experimental sessions were conducted in eight standard operant-conditioning chambers for rats, each enclosed in a melamine sound-attenuating cubicle (Med Associates, VT). Each chamber contained a working area of 30.5 cm by 24.1 cm by 21.0 cm, a grid floor, and a 45-mg pellet dispenser with a pellet receptacle centered between two standard response levers, which were 11.5 cm apart from each other, 4.8 cm wide, protruded 1.9 cm into the chamber, elevated 8 cm from the grid floor and required a force of at least 0.25 N for a response to be recorded. Two 28-V stimulus lights of 2.5 cm in diameter were approximately 7 cm above each lever. Each chamber had a 28-V houselight on the wall opposite to the wall containing operandum, and a ventilation fan to circulate air and to mask extraneous noise. Equipment was interfaced to a computer and experimental sessions and data collection were programmed and conducted with MedPC-IV (Med Associates, VT).

2.3. Procedure

The delay-discounting task was modeled after methods used by Evenden and Ryan (1996). The task consisted of a discrete-trials choice procedure in which one lever (e.g., left lever) was associated with one food pellet delivered immediately and the other lever (e.g., right lever) was associated with three food pellets presented after a delay that increased across five blocks of eight trials. The outcomes associated with each lever were held constant for each subject but counterbalanced across subjects. The first trial within the first block started after a 15-min blackout period and trials thereafter began every 100 s. The first two trials within a block were forced-choice trials, which allowed for exposure to the outcome associated with each lever. The first forced-choice trial of a block began with the illumination of the houselight and left or right stimulus light (randomly determined by a computer program). The consequence associated with the lever below the illuminated stimulus light was presented if a single response (FR 1) was emitted on that lever. For example, if the illuminated stimulus light was above the left lever (associated with one immediate food pellet), then a single response on that lever would result in one food pellet delivered immediately signaled by a brief houselight flash (0.1 s). After food pellet presentation, the houselight and stimulus light would extinguish until the start of the next trial.

During the second forced-choice trial, the other alternative was presented. For example, the right stimulus light would be illuminated and one response on the lever below the illuminated stimulus light would result in three food pellets after a programmed delay. At the start of the programmed delay the stimulus light was extinguished while the houselight remained illuminated until the delay period had elapsed. Three food pellets were then delivered each signaled by a brief houselight flash (0.1 s) and the chamber was darkened until the start of the next trial.

The last six trials of a block were free-choice trials in which the houselight and both stimulus lights were illuminated at the start of a trial. After a response was emitted on one of the two levers and the associated outcome was presented as in the previous forced-choice trials, all chamber lights were extinguished until the next trial. If, during any trial type, a response was not emitted within 30 s from trial onset, then the trial was scored as an omission and all chamber lights were extinguished until the next trial. After the sixth free-choice trial, the next block of trials began with an increased delay to the three-food-pellet alternative which increased across the five blocks of eight trials (i.e., 0, 2, 4, 8, 16 s). Stable responding was defined as obtaining at least 80% choice for the larger reinforcer during the 0-s delay block and no increasing or decreasing trends in delay-discounting functions via weekly visual inspection. Stability was met between 10 and 20 sessions (consistent with past research; Evenden and Ryan, 1996).

Zero-second probe sessions were implemented every Wednesday, except during the repeated MPH procedure. These 0-s probe sessions consisted of both outcomes (one food pellet and three food pellets) presented immediately following a lever press in all blocks of a

session. A 0-s probe session was sometimes repeated on Thursday and Friday if the stability criterion was not met on Wednesday. Stability during the 0-s probe session was met if choice for the larger reinforcer was at least 80% across all blocks. The 0-s probe sessions were conducted in order to test if choice was sensitive to changes in programmed delays (e.g., Evenden and Ryan, 1996; Pitts and McKinney, 2005; Slezak and Anderson, 2009).

2.4. Drugs

Methylphenidate hydrochloride (Sigma, St. Louis, MO) was dissolved in 0.9% saline solution (1 mg/ml) and was administered intraperitoneally (i.p.) in a volume of 1.0 ml/kg. The doses tested were 1.0, 3.0, 5.6, and 10.0 mg/kg.

2.5. Acute drug administration

Sessions during the acute drug administration phase occurred Monday through Friday at approximately the same time each day. Performance on Monday and Thursday served as control sessions for drug testing on Tuesday and Friday. Before administration of MPH, saline (vehicle or 0.0 mg/kg MPH) was administered i.p. during at least two consecutive drug sessions. Thereafter, at least two determinations of each dose of MPH and saline were obtained and the order of dose presentation was counterbalanced between subjects. Results from drug sessions were not included if there was more than 10 free-choice trial omissions (1/3 of total free-choice trials) in a single session or an entire block of trials were omitted in a single session. This occurred during some determinations of 10.0 mg/kg MPH.

2.6. Repeated drug administration

After the acute dose–response function was determined, saline was repeatedly administered for at least five consecutive sessions and until choice was comparable to baseline responding. As MPH doses are typically titrated to how an individual responds in the clinical setting (Vitiello et al., 2001), the chronic MPH dose administered to each rat was based on individual results. The acute dose that resulted in increases in larger-reinforcer choice relative to saline evident via visual inspection of individual delay-discounting functions was administered repeatedly for 30 sessions (7 days/week). A dose of 3.0 mg/kg MPH was injected repeatedly for SHR-3, SHR-4, SHR-7 and SHR-8, 5.6 mg/kg MPH for SHR-1 SHR-5 and SHR-6, and 10.0 mg/kg MPH for SHR-2.

After 30 sessions of repeated MPH administration, the dose–response function was redetermined with doses tested at least twice during test sessions on Tuesday and Friday. The repeated MPH dose was administered during non-test sessions. After redetermination of the dose–response function, saline was administered repeatedly to observe any residual effects due to cessation of repeated administration of MPH.

2.7. Data analysis

The mean percent choice for the larger reinforcer during each delay value was determined for performance after saline administration and for the acute and chronic effects of MPH. Repeated measures ANOVAs with Dunnett multiple comparison tests were used to analyze the relation between effects of MPH dose and delay duration on percent larger-reinforcer choice during the acute and chronic phase. To conduct the repeated measures ANOVA, a maximum likelihood estimator (the expectation-maximization algorithm) in SPSS 18 was used to estimate performance for SHR-1 and SHR-7 at the chronic 10.0 mg/kg dose. These estimated values were not used for the AUC analysis described below.

By using a method derived from Myerson et al. (2001), the area under the curve (AUC) was calculated as a quantitative index of choice during the delay-discounting task in each condition (acute, chronic and withdrawal). Increases in AUC are consistent with increases in larger-reinforcer choice across all delays, and thus decreases in impulsive choice. AUC was calculated by plotting percent choice (0–100%) for the larger reinforcer (y-axis) as a function of the delays (0, 2, 4, 8, 16 s) to the larger reinforcer (x-axis) and then dropping lines down from each percent larger-reinforcer choice data point to the x-axis creating trapezoids. Next, the area within each trapezoid was calculated and the area of all trapezoids was summed. As a method of standardization, the total trapezoid area was divided by the total area of the graph (e.g., 1600). This measure was utilized as an unbiased quantitative assessment of delay-discounting functions (Myerson et al., 2001). A repeated measures ANOVA was used to compare the acute and chronic AUC dose–response functions. Statistical analysis of the mean differences in AUC between saline and acute MPH administration were conducted using paired *t*-tests as was the comparison between mean differences in AUC between chronic saline and chronic MPH administration. All statistical comparison maintained a significance level of 0.05.

3. Results

Two subjects (SHR-5 and SHR-6) died during two different points of experimentation due to factors not clearly related to the experiment. Subject SHR-5 died during the repeated administration of 5.6 mg/kg MPH and subject SHR-6 died after redetermination of the MPH dose–response function. Therefore, no results are presented for SHR-5 beyond acute effects of MPH, and no results are presented for SHR-6 during withdrawal from chronic MPH administration.

Consistent with previous literature, and as shown by the group means in Fig. 1, as the delay increased (x-axis of Fig. 1), the mean percent choice for the larger reinforcer (y-axis of Fig. 1) decreased after administration of saline. In Fig. 2A (top panel), the mean percent choice for the larger reinforcer is presented as a function of acute MPH dose (1.0–10.0 mg/kg) with separate functions indicating different delays (0–16 s) to the larger reinforcer. After administration of MPH, choice for the larger reinforcer dose dependently increased (larger doses at longer delays) or decreased (larger doses at shorter delays) relative to saline. Thus, the particular effects of acute MPH on choice were dependent upon the delay to the larger reinforcer and the dose administered. This finding is supported by the overall dose-by-delay repeated-measures ANOVA that resulted in a significant dose-by-delay interaction [$F(16,112) = 7.18$, $p < .05$]. It should be noted that some of

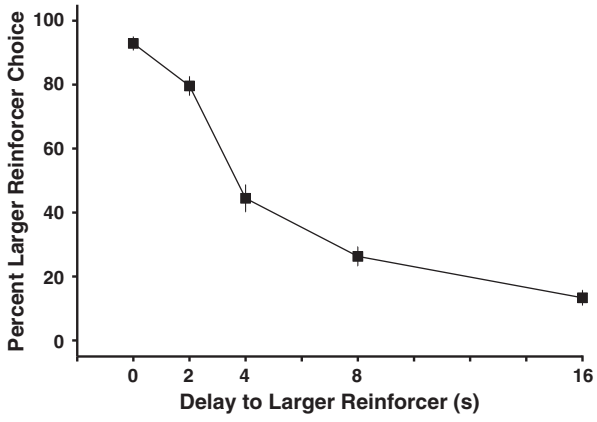

Fig. 1. The group average percent choice for the larger reinforcer as a function of delay after acute administration of saline. Error bars are presented as standard error of the mean.

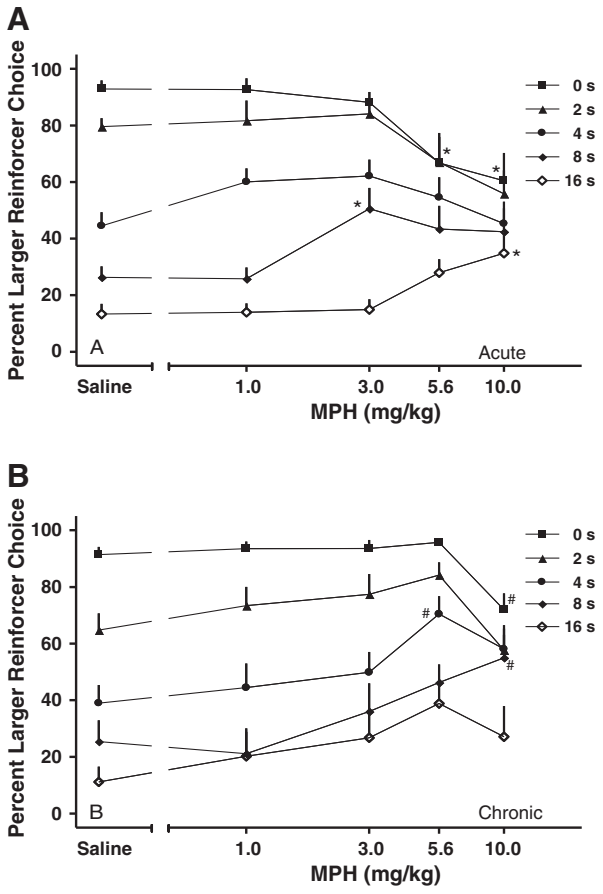

Fig. 2. The top panel (A) shows the group average percent choice for the larger reinforcer (versus the smaller, immediate reinforcer) as a function of dose (1.0 to 10.0 mg/kg MPH) during the acute administration of MPH at each larger-reinforcer delay value (filled square during a 0-s delay, filled triangle during a 2-s delay, filled circle during a 4-s delay, filled diamond during a 8-s delay and open diamond during a 16-s delay). Error bars are presented as standard error of the mean. Statistical significance denoted by *, are between saline and 3.0 mg/kg MPH during the 8-s delay, saline and 5.6 mg/kg MPH during the 16-s delay, and saline and 5.6 and 10.0 mg/kg MPH during the 0-s delay. The bottom panel (B) shows the group average percent choice for the larger reinforcer as a function of dose (1.0–10.0 mg/kg MPH) during the chronic administration of MPH at each delay value as described above. Statistical significance denoted by #, are between saline and 5.6 mg/kg MPH during the 4-s delay, saline and 10.0 mg/kg MPH during the 0-s and 8-s delay.

the changes observed in larger-reinforcer choice were also accompanied by a decrease in control, as choice was disrupted in the 0-s (control) block after 5.6 and 10.0 mg/kg.

Separate repeated measures ANOVA were conducted at each delay value to examine the change in larger-reinforcer choice as a function of dose (seen in Fig. 2A). There was a significant change [$F(4,28) = 3.09$, $p<.05$] in percent larger-reinforcer choice during the 8-s delay block (filled diamond in Fig. 2A) with a significant increase [Dunnett, $p<.05$] in larger-reinforcer choice after administration of 3.0 mg/kg relative to saline. There was also a significant change [$F(4,28) = 4.80$, $p<.05$] during the 16-s delay block (open diamond in Fig. 2A) with a significant increase [Dunnett, $p<.05$] in larger-reinforcer choice after 10.0 mg/kg administration relative to saline. The increase in larger-reinforcer choice found after 10.0 mg/kg administration during the 16-s delay block, however, was accompanied by a decrease in larger-reinforcer choice in the 0-s block (filled square in Fig. 2A). That is, the percent larger-reinforcer choice was significantly different [$F(4,28) = 8.14$, $p<.05$] during the 0-s delay block with significant decreases [Dunnett, $p<.05$] after 5.6 and 10.0 mg/kg administration relative to saline. In summary, the particular changes in larger-reinforcer choice were dependent on both the dose of MPH administered and the delay to the larger reinforcer. Administration of a relatively low MPH dose resulted only in an increase in larger-reinforcer choice during the 8-s delay block and administration of relatively higher MPH doses resulted in both increases (16-s delay block) and decreases (0-s delay block) in choice.

The average AUC after acute administration of each MPH dose is depicted in Fig. 3 (filled squares) to show the global change in larger-reinforcer choice across all delays. The AUC analysis indicates that overall larger-reinforcer choice significantly increased after acute administration of 3.0 mg/kg MPH ($M = 0.52$, $SEM = 0.05$) relative to saline ($M = 0.37$, $SEM = 0.03$; $t(7) = 2.96$, $p<.05$). The AUC analysis is consistent with results found in the analysis of larger-reinforcer choice during each delay block after acute MPH administration.

The MPH dose–response function was redetermined following 30 sessions of chronic MPH administration. Fig. 2B (bottom panel) shows the percent choice for the larger reinforcer as a function of MPH dose (1.0–10.0 mg/kg) with separate functions that indicate different delays (0–16 s) to the larger reinforcer. Similar to the acute dose–response function, administration of MPH resulted in both increases and decreases in choice for the larger reinforcer relative to saline conditions that were dependent upon the delay to the larger reinforcer and the dose administered. This finding is supported as the overall dose-by-delay repeated-measures ANOVA resulted in a significant dose-by-delay interaction [$F(16,96)$, 3.81, $p<.05$]. Separate repeated measures ANOVA were conducted at each delay value to analyze changes in larger-reinforcer choice as a function of dose (seen in Fig. 2B). There was a significant change [$F(4,24) = 3.29$, $p<.05$] during the 4-s delay block (filled circle in Fig. 2B) with a significant increase [Dunnett, $p<.05$] in larger-reinforcer choice after 5.6 mg/kg administration relative to saline. In addition, there was a significant change [$F(4,24) = 3.41$, $p<.05$] during the 8-s delay block (filled diamond in Fig. 2B) with a significant increase [Dunnett, $p<.05$] in larger-reinforcer choice after 10.0 mg/kg administration relative to saline. There was also a significant change [$F(4,24) = 10.05$, $p<.05$] during the 0-s block (filled square in Fig. 2B) with a significant decrease [Dunnett, $p<.05$] in larger-reinforcer choice after 10.0 mg/kg administration relative to saline. In summary, administration of 5.6 mg/kg MPH resulted in an increase in mean larger-reinforcer choice during the 4-s delay block, and administrations of 10.0 mg/kg MPH resulted in an increase (8-s delay block) and decrease (0-s delay block). Thus, the particular changes in larger-reinforcer choice after chronic MPH administration were dependent on both the dose of

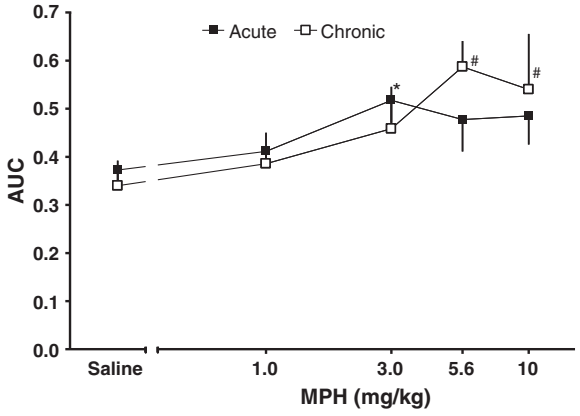

Fig. 3. Group mean AUC for the acute dose–response function (filled square) of 1.0 to 10.0 mg/kg MPH and saline ($n = 8$ at each dose) and for the chronic dose–response function (open square) of saline and 1.0 to 5.6 mg/kg MPH ($n = 7$) and 10.0 mg/kg MPH ($n = 5$). Error bars are presented as standard error of the mean and point downward for the acute dose–response function and upward for the chronic dose–response function. Statistical significance denoted by *, are between acute saline and acute 3.0 mg/kg MPH. Statistical significance denoted by #, are between chronic saline and 5.6 and chronic saline and 10.0 mg/kg MPH.

MPH administered and delay to the larger reinforcer, which is congruent with the acute MPH effects on choice. It should be noted that some of the control lost in the 0-s (control) block during acute MPH administration (5.6 and 10.0 mg/kg) recovered during chronic MPH administration.

The analysis of AUC as a global change in larger-reinforcer choice during the chronic regimen is presented in Fig. 3 (open squares). Significant increases in AUC were found between 5.6 mg/kg MPH ($M=0.59$, $SEM=0.05$) and saline ($M=0.34$, $SEM=0.05$; $t(6)=3.58$, $p<.05$) and 10.0 mg/kg MPH ($M=0.54$, $SEM=0.12$) and saline ($M=0.36$, $SEM=0.07$; $t(4)=2.81$, $p<.05$). The acute and chronic AUC dose–response functions were also compared, but no significant differences were observed [$F(4,16)=2.53$, $p=.081$].

After cessation of the chronic MPH regimen, the AUC determined for the first five sessions of withdrawal or repeated saline administration ($M=0.25$, $SEM=0.07$), while lower than the AUC after acute saline administration ($M=0.35$, $SEM=0.04$), was not significantly different. This return to baseline suggests no long-term changes in impulsive choice after repeated MPH exposure. AUC for individual subjects across acute, chronic, and withdrawal conditions are presented in Table 1.

4. Discussion

4.1. Acute MPH effects

MPH is a first-line treatment for the symptoms of ADHD in humans, which include inattention and/or impulsivity and hyperactivity. As the treatment and diagnosis of ADHD spans from childhood through adulthood, it has become especially critical to assess long-term effects of ADHD medications on specific behavioral measures, such as impulsive choice, that has relevance to the disorder. In the present study, one dose, 3.0 mg/kg MPH, acutely increased mean percent-larger reinforcer choice during the 8-s delay block and thus, increased AUC. This outcome is in agreement with past research with humans (Shiels et al., 2009) and nonhuman animals (Pitts and McKinney, 2005; van Gaalen et al., 2006) showing that an acute dose of MPH may significantly decrease impulsive choice. More importantly for the present study, the increases in larger-reinforcer choice found after 3.0 mg/kg MPH administration were not accompanied by decreases in choice during the 0-s delay block which was observed at higher doses. The disruption in choice during the 0-s delay block may provide an alternative account for acute effects of MPH under the current delay-discounting task.

Decreased choice for the larger reinforcer during the 0-s delay block may suggest disruption in stimulus control such as the discrimination between differential reinforcer amounts or delays. The relatively higher acute doses (5.6 and 10.0 mg/kg) of MPH may have been affecting discrimination between the two reinforcer amounts. If discrimination between reinforcer amounts is affected, then it is likely that percent larger-reinforcer choice would converge around 50% across delays. The clearest example of convergence of choice around 50% was after administration of 10.0 mg/kg MPH. There was both a significant increase (during the 16-s delay block) and decrease (during the 0-s delay block) in larger-reinforcer choice in which the mean choice at both delays was approaching 50%. There is also previous experimental evidence showing a decreased choice for the larger reinforcer during a 0-s delay block after acute administration of the psychostimulant D-amphetamine (Slezak and Anderson, 2009). The interpretation that drugs (including stimulants) may be affecting discrimination between reinforcer amounts in an impulsive choice procedure has been proposed before (e.g., Pitts and McKinney, 2005; Locey and Dallery, 2009).

4.2. Repeated MPH effects

A primary goal of the current study was to determine if tolerance (i.e., reduced effectiveness of MPH), sensitization (enhanced effectiveness of MPH) or sustained efficacy is evident after chronic exposure to MPH under an impulsive-choice procedure and if there were any changes in choice after the cessation of chronic drug treatment. Two doses (5.6 and 10.0 mg/kg) were shown to increase mean larger-reinforcer choice at intermediate delays (4 and 8 s, respectively) after chronic administration with the caveat concerning decreases in choice during the 0-s delay block after the 10.0 mg/kg dose (see discussion above). In addition, no significant differences were found between the acute and chronic AUC dose–response functions. The fact that MPH continued to increase larger-reinforcer choice during a chronic regimen and the lack of a statistically significant shift in the dose–response function indicates that MPH administration sustained a decrease in impulsive choice and there was no evidence of tolerance or sensitization. When repeated MPH administration was suspended, no statistically significant changes in larger-reinforcer choice were observed relative to baseline performance indicating no residual effects of chronic MPH. It does show, however, that decreases in impulsive choice were no longer evident after drug cessation suggesting that the therapeutic effect of MPH did not continue when drug administration was terminated. Overall, repeated administration of MPH demonstrated efficacy in sustaining a decrease in impulsive choice, but only at select doses and delays. A larger dose (10.0 mg/kg MPH) disrupted choice during the 0-s delay block, which may provide evidence of decreased stimulus control.

The chronic dose of MPH was determined functionally for each subject, and thus three different doses (3.0, 5.6, and 10.0 mg/kg) were administered repeatedly. The small sample size at each dose, however, precluded a meaningful statistical analysis of whether the chronic MPH doses differentially affected choice during the subsequent redetermination of the dose–response function. Future studies could determine the influence of MPH dose (especially doses within a clinically relevant range) on the long-term effects on impulsive

Table 1
Area under the curve presented for each subject across acute, chronic and withdrawal conditions. Chronic dose is in bold.

Condition	Determination	Subject								Mean	SEM
		SHR-1	SHR-2	SHR-3	SHR-4	SHR-5	SHR-6	SHR-7	SHR-8		
Saline	Acute	0.45	0.25	0.35	0.47	0.39	0.45	0.31	0.31	0.37	0.03
	Chronic	0.36	0.28	0.19	0.26	–	0.49	0.24	0.56	0.34	0.05
	Withdrawal	0.15	0.19	0.56	0.35	–	–	0.15	0.11	0.25	0.07
1.0 mg/kg	Acute	0.41	0.42	0.41	0.57	0.34	0.32	0.43	0.39	0.41	0.03
	Chronic	0.76	0.30	0.26	0.38	–	0.30	0.37	0.33	0.39	0.06
3.0 mg/kg	Acute	0.72	0.48	**0.45**	**0.59**	0.27	0.49	**0.59**	**0.55**	0.52	0.05
	Chronic	0.80	0.58	0.21	0.49	–	0.63	0.19	0.31	0.46	0.09
5.6 mg/kg	Acute	**0.84**	0.46	0.28	0.25	0.49	**0.59**	0.53	0.38	0.48	0.07
	Chronic	0.55	0.36	0.76	0.50	–	0.76	0.60	0.58	0.59	0.05
10.0 mg/kg	Acute	0.37	**0.51**	0.28	0.30	0.42	0.65	0.63	0.72	0.49	0.06
	Chronic	–	0.37	0.43	0.28	–	0.89	–	0.73	0.54	0.12

choice. It may also be important to address differences in the route of administration to examine important pharmacokinetic factors (see Volkow and Insel, 2003 for a discussion). For example, clinical administration of MPH is typically oral, which has a slower absorption rate into the blood stream and to the brain as opposed to parental routes of administration, and may affect behavior differently during a chronic drug regimen.

4.3. MPH and the Spontaneously Hypertensive Rats (SHR)

Dysregulation in the dopaminergric and noradrenergic systems is thought to underlie many of the symptoms of ADHD (e.g., Ernst et al., 1999; Solanto, 1998; Madras et al., 2005). MPH (a catecholamine reuptake inhibitor) is one of the most often prescribed therapeutics to treat ADHD and generally increases levels of dopamine in the brain, but also increases norepinephrine levels as well (Kuczenski and Segal, 2001; Heal et al., 2009). The acute and chronic effects of MPH on impulsive choice were demonstrated in the SHR, which has been proposed to have a hypofunctioning dopamine system and a hyperactive noradrenergic system relative to control subjects (Wistar Kyoto rat, WKY; see Russell et al., 2005). Although not measured in the present study, one mechanism by which MPH may exert its therapeutic benefit (see Krause et al., 2000; Vles et al., 2003 for human studies) is by down-regulation of the dopamine transporter (DAT; reuptakes dopamine from the synapse). Roessner et al. (2010) demonstrated in SHRs that a 14-day treatment of 2 mg/kg oral MPH starting at either PND 25 or PND 50 resulted in reduced striatal DAT density at PND 90 relative to vehicle-treated SHRs. Thus, down-regulation of the DAT may be a mechanism by which MPH continually exerts its therapeutic effect, however, we did not directly measure DAT levels nor did Roessner et al. (2010) correlate the down-regulation of DAT after MPH exposure with changes in behavioral measures relevant to ADHD.

It should also be noted that conclusions that validate the SHR as an animal model of ADHD based on the current findings cannot be made because the suggested control strain (WKY) was not included, although previous research has indicated greater impulsive choice in the SHR compared to the WKY (Adriani et al., 2003; Fox et al., 2008; Sutherland et al., 2009). The assessment of acute administration of psychostimulants (e.g., MPH and D-amphetamine) on impulsive behavior in SHR and WKY rats have been mixed (e.g., see van den Bergh et al., 2006; Bizot et al., 2007; Kantak et al., 2008; Sagvolden and Xu, 2008; Hand et al., 2009), but could be related to variables such as age, choice procedure used, or control substrains. For example, Sagvolden et al. (2009) discussed how some of the discrepancies may be explained by differences in the particular WKY substrain utilized, while others (Drolet et al., 2002; van den Bergh et al., 2006) have questioned the utility of the WKY as a control strain in general.

5. Conclusion

In the present study, effects of MPH, a first-line ADHD therapeutic, on impulsive choice were assessed in the SHR across acute and chronic administration. Past research with human and nonhuman animals was replicated in that MPH administration led to a decrease in impulsive choice; however, decreases in impulsive choice after acute and chronic administration were only found at one of four delays (8 and 4 s, respectively), at one of four doses (3.0 and 5.6 mg/kg, respectively) that were not accompanied by decreases in larger-reinforcer choice during the 0-s delay. Choice maintained by the larger reinforcer at relatively higher doses during acute and chronic administration was disrupted when there was no delay to either outcome providing evidence that relatively high doses of MPH may be affecting stimulus control. Overall, chronic administration of MPH demonstrated efficacy in sustaining decreases in impulsive choice, but only at select doses and delays.

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