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ORIGINAL INVESTIGATION

Methylphenidate and impulsivity: a comparison of effects of methylphenidate enantiomers on delay discounting in rats

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Abstract
Rationale Current formulations of methylphenidate (MPH) used in treatment of attention-deficit/hyperactivity disorder (ADHD) result in significantly different bioavailability of MPH enantiomers. Daytrana®, a *dl*-MPH transdermal patch system, produces higher levels of *l*-MPH than when *dl*-MPH is administered orally (e.g., Ritalin®). One potential limitation of increased *l*-MPH was indicated in a preclinical study showing *l*-MPH may attenuate effects of *d*-MPH.
Objectives The objective of the study was to investigate the interactive effects of MPH enantiomers by (1) assessing drug effects via a preclinical model of "impulsivity" and (2) performing a quantitative dose equivalence analysis of MPH enantiomer interactions.
Methods Sprague–Dawley rats were trained to emit either of two responses, one producing an immediate food pellet, the other producing four pellets delivered at increasing delays (0, 8, and 32 s). The percent selection of the larger food amount was graphed as a function of delay with the area under the curve (AUC) assessed. Increases in AUC are consistent with decreases in "impulsivity" (i.e., selection of the smaller, immediate over the larger, delayed reinforcer).
Results Systemic administration of *dl*-MPH and *d*-MPH dose-dependently increased AUC, while *l*-MPH, morphine, and pentobarbital did not alter AUC. An analysis based upon dose equivalence indicated that *dl*-MPH produced additive effects that were not different from that predicted from effects of the enantiomers administered alone.
Conclusions The present results indicate pharmacologically selective effects in that only drugs prescribed for the treatment of ADHD symptoms decreased a measure of "impulsivity" and that *l*-MPH likely does not attenuate or enhance the effects of *d*-MPH in the current delay-discounting task.

Keywords Methylphenidate · Psychostimulants · Delay discounting · Impulsivity · Enantiomers · Dose equivalence · ADHD · Rat

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurobehavioral disorder among children (6–9 %) and adults (3–5 %) in the USA (Dopheide and Pliszka 2009). Psychostimulant administration (i.e., methylphenidate and amphetamine) has been the mainstay of clinical treatment in both children and adults for alleviating the core behavioral symptoms of inattention, impulsivity, and hyperactivity. Methylphenidate (MPH) is composed of two pairs of enantiomers (*erythro* and *threo*), of which the latter pair (*d-threo*- and *l-threo*-MPH; hereafter referred to as *d*-MPH and *l*-MPH, respectively) is currently used in the treatment of ADHD.

There are at least three different commercial formulations of MPH, and each result in unique relative amounts of enantiomers (*d*-MPH and *l*-MPH) that are absorbed into systemic circulation. Ritalin® is composed primarily of *dl*-MPH; however, only 10–52 % of *dl*-MPH reaches systemic circulation after oral administration due to gastrointestinal absorption and first-pass metabolism in the liver (Chan et al. 1983). Further, disposition is enantioselective as the maximum drug concentration of *d*-MPH was found to be approximately seven times higher than *l*-MPH at a 10-mg dose (Srinivas et al. 1987).

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Thus, after oral administration, approximately less than half of *dl*-MPH reaches systemic circulation and only a small proportion is the *l*-enantiomer. A second commercial formulation of oral MPH (Focalin®) was subsequently developed to contain only the *d*-enantiomer of MPH, in part because of the low bioavailability of *l*-MPH found with oral administration of *dl*-MPH. In addition, preclinical assessments indicate that *d*-MPH has a greater binding affinity for the dopamine and norepinephrine transporters (Patrick et al. 1987), and its administration results in larger peak increases in extracellular dopamine and norepinephrine (Kuczenski and Segal 1997; Heal et al. 2008) and greater stimulation of locomotor activity (Patrick et al. 1987) relative to *l*-MPH. Thus, the *d*-enantiomer appears to be more pharmacologically active, in particular when *dl*-MPH is administered orally for clinical treatment. However, a third MPH formulation, known commercially as Daytrana®, is primarily composed of *dl*-MPH, but is delivered via a transdermal patch system. As this system avoids first-pass metabolism, higher concentrations of *l*-MPH are available in systemic circulation (~60–70 % of the maximum concentration of *d*-MPH; Anderson and Scott 2006). Therefore, oral and transdermal administration of *dl*-MPH results in substantially different levels of *l*-MPH, and the contribution of the *l*-enantiomer to the behavioral effects of *dl*-MPH deserve further attention as related to the treatment of ADHD.

There are few studies that have assessed behavioral effects of MPH enantiomers in preclinical animal or procedural models of ADHD. Davids et al. (2002) determined the extent to which each MPH enantiomer alone (0.3–10.0 mg/kg) or in combination could reduce motor hyperactivity in juvenile rats with neonatal 6-hydroxydopamine (6-OHDA) lesions of forebrain dopamine projections. Administration of *d*-MPH was found to be 3.3 times more potent than *dl*-MPH in reducing locomotor activity, while *l*-MPH alone was without effect. Pretreatment with 10.0 mg/kg *l*-MPH resulted in an attenuation of the reduced hyperactivity seen after administration of 10.0 mg/kg *d*-MPH, suggesting that *l*-MPH modulates the effects of *d*-MPH.

The present study was designed to investigate the generalizability of the previously documented interactive effects of MPH enantiomers to a procedural model of "impulsivity" and identify the pharmacological specificity of such effects. This was accomplished by determining the effects of each MPH enantiomer alone and in combination (i.e., *dl*-MPH) on a delay-discounting task. With this task, an impulsive choice is operationally defined as selection of a smaller, immediate reinforcer over a larger, delayed reinforcer. A drug prescribed for ADHD treatment (e.g., *dl*-MPH) should increase selection of the larger, delayed reinforcer (cf. Pitts and McKinney 2005; van Gaalen et al. 2006; Paterson et al. 2011; Slezak and Anderson 2011) and drugs not prescribed for ADHD treatment should not increase larger reinforcer selections. For example, morphine (a mu opioid agonist) has not demonstrated therapeutic application for ADHD treatment and has been found to decrease selection of the larger, delayed reinforcer in delay-discounting studies with rats (e.g., Kieres et al. 2004; Pitts and McKinney 2005). Effects of the barbiturate pentobarbital, which has not been investigated in a delay-discounting paradigm, were also determined as a negative control. A dose equivalence analysis (Tallarida and Raffa 2010) was conducted to determine if the observed effects of the enantiomers combined produce an effect greater than (synergism), less than (subadditivity), or equal to (additivity) the expected effect derived from the observed effects of each enantiomer administered alone. This quantitative assessment provides an indication of MPH enantiomer interactions, which is currently of importance as the *dl*-MPH patch system Daytrana® results in a considerable increase in exposure to the *l*-enantiomer previously not observed with oral administration of *dl*-MPH.

Methods

Subjects Male Sprague–Dawley rats (Taconic Farms, Hudson, NY, USA) served as subjects and weighed 325–350 g. Subjects (n=5) were housed individually under a 12-h light/dark cycle with water continuously available in their home cage. Subjects were fed approximately 8–12 g of rat chow 1 h after each session, resulting in approximately 22 h of food restriction before the start of each experimental session.

Apparatus Sessions were conducted in two-lever operant conditioning chambers (modified ENV 007, Med Associates, Inc., St. Albans, VT, USA) housed within sound-attenuating cubicles (ENV-018, Med Associates, Inc.). A downward force on the lever (approximately 0.4 N) through approximately 1 mm defined a response and produced an audible click. The chambers contained two pairs of light-emitting diodes (LEDs) directly above each lever, a houselight at the ceiling above each pair of LEDs, and a food receptacle behind an approximately 5×5 cm opening centered in the front panel. A dispenser (ENV-203, Med Associates, Inc.) behind the front panel delivered 45-mg food pellets (Bio-Serv, Inc., Frenchtown, NJ, USA) into the receptacle. White noise masked extraneous sounds.

Procedure Experimentally naïve subjects were trained to lever press via reinforcement of successive approximations to the target response (left lever press for three subjects and a right lever press for two subjects). Once pressing, a fixed-ratio 1 schedule of reinforcement alternated on each lever to further establish pressing and switching between levers for approximately five sessions of 40 food pellets each. Subsequent training was conducted with different outcomes for pressing the two levers as per Evenden and Ryan (1996) and modification by Cardinal et al. (2000). Daily sessions (Monday to Friday) consisted of three blocks of 14 trials in which the emission of

one response on one of the levers produced an immediate single 45-mg food pellet whereas a response on the other lever produced four food pellets delivered after increasing delays. The delay to the larger reinforcer increased sequentially (i.e., 0-, 8-, and 32-s delays) across blocks of 14 trials.

The first four trials of each block were forced exposure trials in which the houselight was illuminated and the LEDs above only one of the two levers (randomly determined) were either constantly illuminated (correlated with one, immediate food pellet) or flashed (correlated with four, delayed food pellets). The flash rate was 30-, 3-, and 0.3-s on/off, during the 0-, 8-, and 32-s delay block, respectively. If the outcome was four delayed pellets, the LEDs were extinguished and the houselights were flashed (0.5 s on/off) for the duration of the delay (i.e., a signaled delay). If the outcome was one immediate pellet, a response produced the food pellet and the houselights and LEDs were extinguished. If a lever press did not occur within 30 s of trial onset, the trial was recorded as an omission and all lights were extinguished until the next trial. The chamber was dark between all trials. Trials started every 40-, 48-, and 72-s during the 0-, 8-, and 32-s delay block, respectively, so that the rate of reinforcer delivery was constant within a block of trials. During the last ten trials of each block, LEDs were illuminated above both levers and a single lever press resulted in either a single pellet or four delayed pellets with all other conditions as described above.

Stable performance was defined as at least 80 % selection of the larger reinforcer during the 0-s delay block across five consecutive sessions. In addition, there was no more than 20 % variation in selection of the larger reinforcer within each delay block across the same five sessions. One subject consistently had about 30 % variation within the 32-s delay block only. As there was no trend in this value across sessions, drug studies were initiated with that subject as well. A minimum of 20 sessions were conducted before drugs were tested. Sessions in which the delay to the larger reinforcer was 0 s in each block were occasionally implemented in facilitation of training and were discontinued during the period of drug assessment.

Drugs *dl*-Methylphenidate HCl, *d*-methylphenidate HCl, *l*-methylphenidate HCl, morphine SO_4, and pentobarbital Na (Sigma-Aldrich, St. Louis, MO, USA) were dissolved in a 0.9 % NaCl solution and injected i.p. (1 ml/kg) 15 min before sessions on Tuesdays and Fridays. All doses refer to milligrams of the salt forms per kilogram body weight. Each dose of drug was tested in a pseudorandom order with the exception that no dose was tested a second time until all doses were tested once. The drugs were tested in the following order: *dl*-MPH, morphine, *d*-MPH, *l*-MPH, *dl*-MPH, and pentobarbital and occurred over a period of approximately 10 months.

Data analysis The percentage of trials in which the larger reinforcer was selected (i.e., number of larger reinforcer selections/number of trials with a response) for each delay block was determined. Area under the curve (AUC) of percentage of larger reinforcer selections as a function of delay was used to provide an unbiased quantitative assessment of delay discounting (Myerson et al. 2001). Increases in AUC are consistent with increases in selection of the larger reinforcer. AUC was calculated by plotting percent larger reinforcer selections (*y*-axis) as a function of delay (*x*-axis) and then applying the trapezoidal rule (Iserles 1996). In addition, response latency (i.e., time from trial onset to a response) and trial omissions (i.e., no response within 30 s of trial onset) were also determined for each delay block.

A three-way repeated measures ANOVA was conducted to compare the difference between the two determinations of *dl*-MPH using percent larger reinforcer selections, latency, and trial omissions as dependent variables. Two-way repeated measures ANOVA were conducted for *d*-MPH, *l*-MPH, morphine, and pentobarbital using percent larger reinforcer selections, latency, and trial omissions as dependent variables. In addition, a one-way repeated measures ANOVA was conducted for each drug with AUC as the dependent variable. Multiple comparison corrected tests were conducted using the Bonferroni method comparing effects of each dose to vehicle–control values and these comparisons were carried out regardless of p values from the overall ANOVA (Hsu 1996; Huck 2009). Significant differences for all analyses were based upon $p<0.05$. It is important to note that the highest dose of *d*-MPH (10.0 mg/kg) and morphine (5.6 mg/kg) was not included in the statistical analysis of percent larger reinforcer selection, latency, or AUC due to a reduced sample size as two and three subjects omitted all trials after 10.0 mg/kg *d*-MPH and 5.6 mg/kg morphine, respectively.

From the AUC dose–effect curves of the individual MPH enantiomers, the expected effect (E_{exp}) of each combination was calculated as the "additive effect" of the enantiomers administered alone based on the concept of dose equivalence, which is used in isobolographic analyses (Tallarida and Raffa 2010). Change in AUC (saline effect subtracted from the dose effect) was calculated for both the expected and the observed change. A paired-samples *t* test was used to compare the mean of the observed change and the mean of the expected change in AUC from the four doses of *dl*-MPH. This analysis determined whether effects of *dl*-MPH produced an effect greater than (synergism), less than (subadditivity), or equal to (additivity) E_{exp}.

Results

Delay discounting was observed in that selection of the larger reinforcer decreased with increases in delay as shown, for example, by performances after saline administration in

Fig. 1 (top panels, points above "Saline"). Additionally, latency values and the frequencies of omissions were not significantly related to delay value.

No significant differences in selection of the larger reinforcer, response latency, or trial omissions were found between the first and second determinations of *dl*-MPH; therefore, the two determinations were averaged for each dependent variable. Administration of *dl*-MPH resulted in a dose-dependent change in percent selection of the larger reinforcer that was also dependent on delay value ($F(8, 32)=5.69$, $p<0.001$; Fig. 1, left column). Specifically, larger reinforcer selections increased at the 8-s delay (triangles) after *dl*-MPH doses of 3.0 mg/kg and greater (all p values <0.001) and at the 32-s delay (circles) after doses of 5.6 mg/kg ($p=0.009$) and 10.0 mg/kg ($p<0.001$). There was also a significant change in response latency ($F(4, 16)=4.56$, $p=0.012$) and trial omissions ($F(4, 16)=9.28$, $p<0.001$) as both dependent variables increased after the highest dose of *dl*-MPH was tested (10.0 mg/kg; p values <0.050). Thus, at doses of 3.0 and 5.6 mg/kg *dl*-MPH, selection of the larger reinforcer increased, but performance was not significantly altered on other measures of behavior such as response latency and trial omissions.

Similar to the effects of the racemate, *d*-MPH administration (Fig. 1, middle column) resulted in a dose- and delay-dependent increase in larger reinforcer selections. The overall ANOVA approached significance ($F(6, 24)=2.12$, $p=0.088$), and Bonferroni-corrected comparisons between dose effects at each delay and performance after vehicle administration resulted in a significant increase in larger reinforcer selections at the 8-s delay (3.0 and 5.6 mg/kg; p values <0.050; Fig. 1, middle column, triangles) and at the 32-s delay (5.6 mg/kg; $p<0.050$; circles). Further, there were significant effects on response latency ($F(3, 12)=4.57$, $p=0.024$) and the number of trial omissions ($F(4, 16)=4.21$, $p=0.016$) as both indices increased after *d*-MPH at 5.6 and 10.0 mg/kg, respectively (p values <0.050). Unlike racemic and *d*-MPH, administration of *l*-MPH (Fig. 1, right column) was largely without effects on the behavior examined. There were no significant effects of dose or delay value on percent selection of the larger reinforcer, nor were there significant effects on response latency or trial omissions.

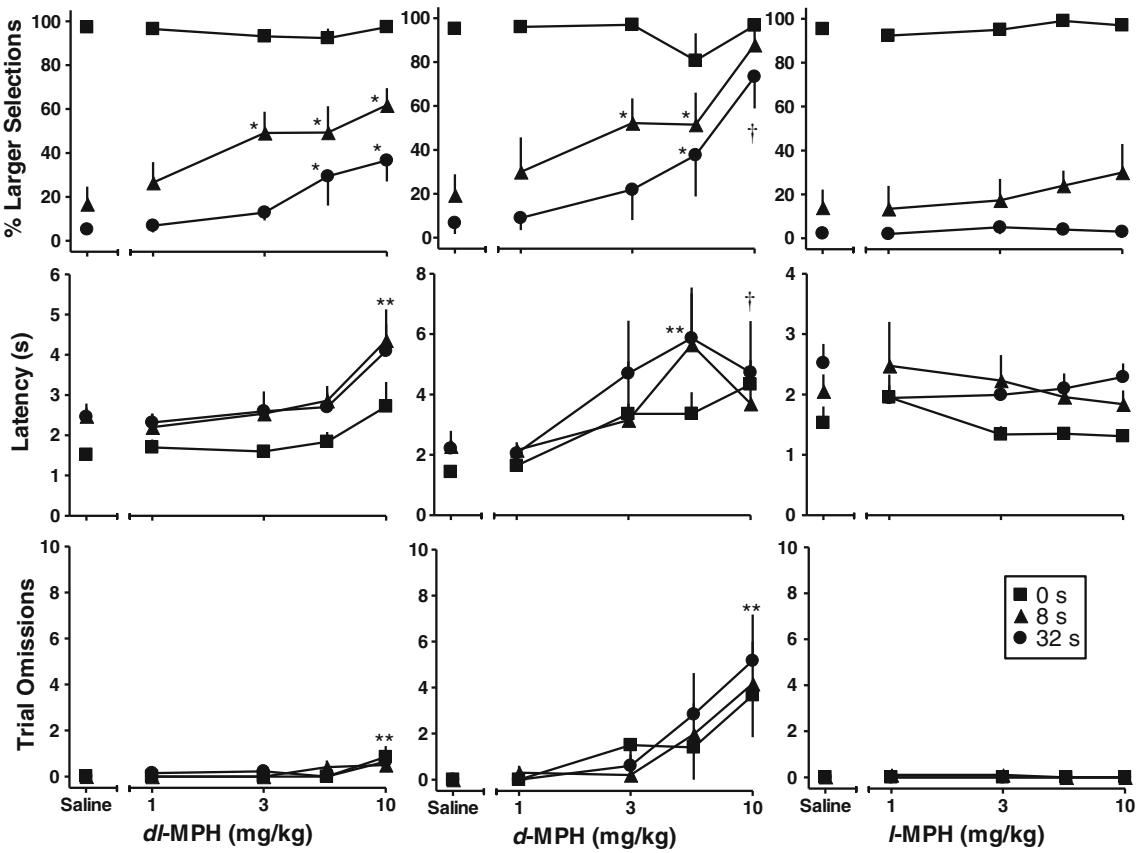

Fig. 1 Effects of *dl*-MPH (*left column*), *d*-MPH (*center column*), and *l*-MPH (*right column*) on percent larger reinforcer selections, response latency (in seconds), and trial omissions are presented as a function of dose (in milligrams per kilogram). Within each panel, there are three functions representing the different larger reinforcer delays (*filled square* for the 0-s delay, *filled triangle* for the 8-s delay, and *filled circle* for the 32-s delay). The sample size at 10.0 mg/kg *d*-MPH for percent larger reinforcer selections and response latency is three due to two subjects omitting all trials and is denoted by a *dagger*. *Error bars* are presented as standard error of the mean. Significant multiple-comparison corrected tests for a particular dose are denoted by *double* asterisks and a particular dose and delay are denoted by a *single* asterisk

Morphine produced a dose-related decrease in selection of the larger reinforcer at the 0-s delay (Fig. 2, left column, squares). Although there was a significant interaction between dose and delay ($F(6, 24)=2.72$, $p=0.037$), Bonferroni-corrected comparisons between dose effects at each delay and performance after vehicle administration were not significant. Morphine produced significant increases in response latency ($F(3, 12)=6.40$, $p=0.008$) and trial omissions ($F(4, 16)=4.84$, $p=0.009$) as both indices increased after 3.0 and 5.6 mg/kg morphine administration, respectively (p values <0.050). Pentobarbital (Fig. 2, right column) resulted in changes in each measure after administration of the highest dose tested (10.0 mg/kg). A dose×delay interaction ($F(8, 32)=6.09$, $p<0.001$) indicated that selection of the larger reinforcer decreased at the 0-s delay and increased at the 8-s delay (p values <0.050). In addition, significant increases in response latency ($F(4, 16)=12.55$, $p<0.001$) and trial omissions ($F(4, 16)=10.01$, $p<0.001$) were obtained at 10.0 mg/kg (p values <0.050).

Both *dl*-MPH and *d*-MPH dose-dependently increased area under the curve of larger reinforcer selections as a function of delay (Fig. 3, top left panel). Both *dl*- and *d*-MPH significantly increased AUC ($F(4, 16)=7.97$, $p<0.001$ and $F(3, 12)=4.15$, $p=0.031$, respectively). Multiple comparison corrected tests indicated that AUC was significantly increased at 5.6 and 10.0 mg/kg of *dl*-MPH and 5.6 mg/kg of *d*-MPH (p values <0.050) compared to vehicle values. In contrast, AUC was not significantly altered after administration of *l*-MPH, morphine, or pentobarbital up to doses of the latter two drugs that increased trial omissions. The observed change in AUC with *dl*-MPH was similar to that expected based on the additive effects (E_{exp}) of the enantiomers combined (Fig. 4). The comparison shows that across the range of 1.0–10.0 mg/kg, the observed effects of the racemic compound were not significantly different from those expected on the basis of additivity of doses of the enantiomers ($t(3)=1.71$, $p=0.187$).

Discussion

Racemic MPH (*dl*-MPH) has been the most common formulation of MPH treatment for ADHD to date. A number of pharmacokinetic and pharmacodynamic studies have indicated that the *d*-enantiomer may solely mediate the therapeutic

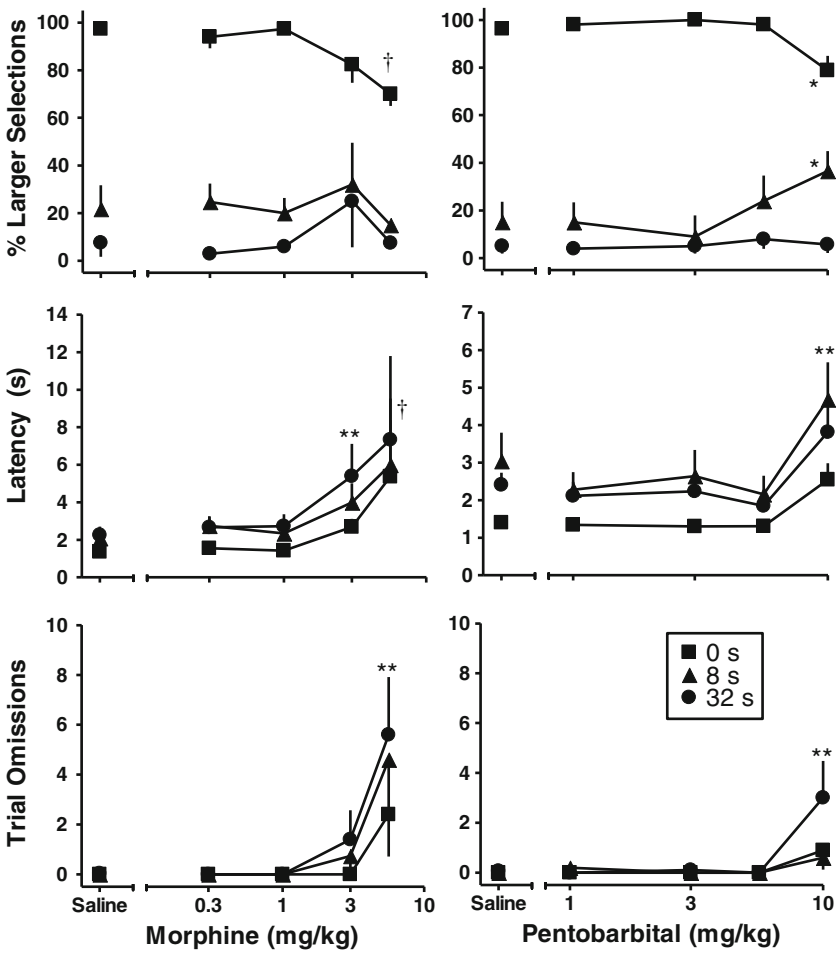

Fig. 2 Effects of morphine (*left column*) and pentobarbital (*right column*) on percent larger reinforcer selections, response latency (in seconds), and trial omissions are presented as a function of dose (in milligrams per kilogram). Within each panel there are three functions representing the different larger reinforcer delays (*filled square* for the 0-s delay, *filled triangle* for the 8-s delay, and *filled circle* for the 32-s delay). The sample size at 5.6 mg/kg morphine for percent larger reinforcer selections and response latency is two due to three subjects omitting all trials and is denoted by a *dagger*. *Error bars* are presented as standard error of the mean. Significant multiple-comparison corrected tests for a particular dose are denoted by *double* asterisks and a particular dose and delay are denoted by a *single* asterisk

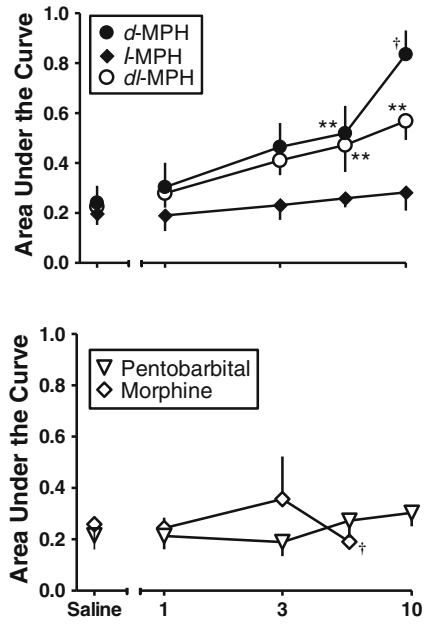

Fig. 3 Effects of *dl*-MPH (*top panel*; *open circle*), *d*-MPH (*top panel*; *filled circle*), *l*-MPH (*top panel*; *filled diamond*), morphine (*bottom panel*; *open diamond*) and pentobarbital (*bottom panel*; *open upside down triangle*) on AUC is presented as a function of dose (in milligrams per kilogram). Sample size is two and three within the AUC panel at 5.6 mg/kg morphine and 10.0 mg/kg *d*-MPH, respectively and is denoted by a *dagger*. *Error bars* are presented as standard error of the mean. Significant multiple-comparison corrected tests for a particular dose are denoted by *double* asterisks

effects of the racemate (see reviews by Heal and Pierce 2006; Markowitz and Patrick 2008). However, results described above (Davids et al. 2002) suggest that the effects of *l*-MPH inhibit the effects of *d*-MPH, which is currently of significance as the *dl*-MPH patch system Daytrana® results in a considerable increase in exposure to the *l*-enantiomer. As in the study by Davids et al., the present study showed that *d*-MPH was more effective over the range of doses studied than *dl*-MPH, whereas *l*-MPH had only small statistically insignificant effects. A further analysis, based on the concept of dose equivalence, was conducted to determine the extent of interaction between the two MPH enantiomers. The obtained effects of

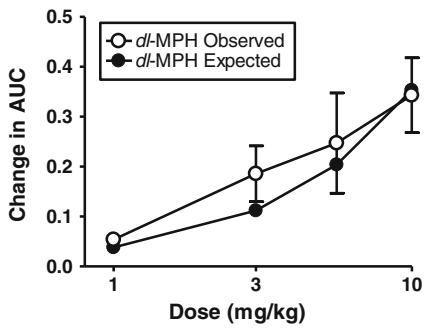

Fig. 4 The change in AUC (saline effect subtracted from the dose effect) is presented as a function of dose for the observed effect of *dl*-MPH (*open circle*) and the expected effect of *dl*-MPH derived from the observed effect of each enantiomer administered alone (i.e., a dose equivalence analysis). *Error bars* are presented as standard error of the mean

dl-MPH on AUC were determined to be no different from the effects predicted from each enantiomer alone. Thus, *l*-MPH likely did not attenuate or enhance effects of *d*-MPH in the present study. The apparent difference between the current findings and those reported by Davids et al. may be related to differences in the behavior examined (locomotor activity vs. delay-discounting performance), animals used (6-OHDA-lesioned rats vs. Sprague–Dawley rats), or evidence used to draw conclusions (ED_{50} values and a pretreatment study with one dose of *l*-MPH vs. the present analysis based upon dose equivalence).

The various mechanisms by which psychostimulants affect behavior in delay-discounting tasks (see Cardinal et al. 2000; Pitts and McKinney 2005; Slezak and Anderson 2009; Huskinson et al. 2012 for detailed discussions) include affecting discrimination between different reinforcer magnitudes and increasing the estimation of time passed (Meck 1983). The former is unlikely in the current study as MPH enantiomers did not significantly affect performance in the no delay block. As more fully discussed by Pitts and McKinney (2005), the latter hypothesis may predict that MPH would increase selection of the smaller, immediate reinforcer, which is opposite to the current findings. Another hypothesis suggests that psychostimulants are decreasing sensitivity to reinforcer delay (e.g., Ta et al. 2008), thus leading to increases in selection of the larger, delayed reinforcer, which is consistent with the present findings.

An additional hypothesis that has been suggested to be related to outcomes during some delay-discounting procedures involves conditioned reinforcement. The distinct signal present during the delay period (a flashing houselight) may have acquired conditioned reinforcing effects, and psychostimulants have been proposed to enhance the effectiveness of conditioned reinforcers (Hill 1970; Robbins 1976). Cardinal et al. (2000) concluded that the presence of a signal during the delay enhanced selection of the larger reinforcer after *d*-amphetamine administration while its absence resulted in a decrease in selection of the larger reinforcer. Alternatively, Slezak and Anderson (2009) found that the effects of *d*-amphetamine did not interact with the presence or absence of a signaled delay (see also Thomas et al. 2009) under conditions with ascending and descending reinforcer delay presentations. It also important to note that the stimulus conditions correlated with the delay were never demonstrated to function as a conditioned reinforcer in the present study or in past research (Cardinal et al. 2000; Slezak and Anderson 2009); thus, further investigation is warranted into the role of conditioned reinforcement in the effects of psychostimulants under delay-discounting tasks.

The pharmacological specificity demonstrated in the present study is consistent with current ADHD pharmacotherapy. Both *dl*-MPH and *d*-MPH administration decreased "impulsivity" as indicated by increases in AUC, while drugs without presumed efficacy in the treatment of ADHD, morphine and

pentobarbital, lacked effects on AUC. These findings support enantioselective effects of MPH and the predictive validity of the current delay-discounting task to assess ADHD medications. However, the predictive validity of the delay-discounting model, in general, as a tool to assess novel ADHD medications is limited based upon inconsistent effects across both positive and negative pharmacological controls and is in need of further consideration. For example, acute administration of *dl*-MPH has been found to increase selection of a larger reinforcer in delay-discounting procedures similar to the one used in the current study (Pitts and McKinney 2005; van Gaalen et al. 2006; Paterson et al. 2011), and the increase in selection of larger reinforcers has been found to persist during chronic *dl*-MPH administration in an ADHD animal model (the spontaneously hypertensive rat; Slezak and Anderson 2011). However, variants of delay-discounting tasks (e.g., adjusting-delay or T-maze tasks) have shown different outcomes with *dl*-MPH (Wooters and Bardo 2011; Bizot et al. 2007, respectively). There have been limited direct comparisons among variants of delay-discounting tasks to determine differences that may contribute to variations in behavioral outcomes. A within-subject comparison of discounting using an adjusting-delay and adjusting-amount procedure in pigeons revealed no systematic differences between the discounting estimates (Green et al. 2007). Similar studies with drugs aimed at assessing the convergent validity of the various delay-discounting procedures will be of value (see also Green and Myerson 2013).

Another potential limitation of the current delay-discounting procedure is the possibility of subjects developing a pattern of switching from the larger reinforcer lever to the smaller reinforcer lever as a function of session duration that is independent of delay and is rather related to a history of the same ascending order of delay presentation during daily sessions. Slezak and Anderson (2009) however found that increasing the variability in delay presentation (i.e., a pseudorandom alternation of ascending and descending delay presentations between sessions) to reduce potential fixed patterns of switching still resulted in similar AUC values for both delay orders and produced similar acute effects of *d*-amphetamine.

Overall, the effects of MPH enantiomers in the present study are consistent with the current understanding of ADHD treatment with MPH as *d*-MPH, but not *l*-MPH, altered the discounting function in a similar manner to *dl*-MPH. Further, delay-discounting procedures in nonhuman animals have translational potential for ADHD-related studies in humans. For example, administration of oral long-acting *dl*-MPH (~0.3 and 0.6 mg/kg) has been found to increase the AUC of discounting functions when the reinforcers and delays used in the task were experienced, but not when they were hypothetical (Shiels et al. 2008). Further experimental analyses directed at identifying the variables commonly affecting the performances of human and nonhuman subjects would be useful for the development of delay-discounting procedures as models for the discovery of improved medications for ADHD.

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