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Methylphenidate as a Reinforcer for Rats: Contingent Delivery and Intake Escalation

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Abstract

Methylphenidate (MPH) is one of the most widely prescribed drugs for treating attention deficit hyperactivity disorder. Previous research suggests that MPH is a reinforcer for rats, but not all of the necessary manipulations to show that lever pressing is controlled by the contingency to obtain MPH have been examined. In Experiment 1, responding for MPH on a progressive ratio (PR) schedule was assessed. Rats self-administered varying doses of MPH (0.056–1.0 mg/kg/infusion) on a PR schedule of reinforcement, and self-administered more MPH than saline, with maximal responding occurring at a unit dose of 0.56 mg/kg/infusion. Experiment 2 examined if there were differences in responding between contingent and non-contingent MPH (0.56 mg/kg/infusion) on an FR schedule of reinforcement. Results showed that rats responded for contingent MPH, and that responding was not maintained when MPH was delivered non-contingently. Experiment 3 examined self-administration of MPH (0.1 or 0.3 mg/kg/infusion) during long access sessions (6 hrs) compared to short access sessions (1 hr). Results showed that rats given long access to MPH showed an escalation of intake across sessions, with this escalation being more pronounced at the lower unit dose (0.1 mg/kg/infusion); in contrast, rats given short access to MPH did not show an increase in MPH self-administration across sessions at either MPH dose tested. Taken together, these results indicate that MPH is an effective i.v. reinforcer for rats and that, similar to other stimulants such as cocaine, amphetamine and methamphetamine, MPH is subject to abuse as reflected by dysregulated intake across repeated long access sessions.

Keywords

methylphenidate; self-administration; rat; progressive ratio; non-contingent; escalation

Introduction

Methylphenidate (MPH) is one of the most widely prescribed drugs for treating attention deficit hyperactivity disorder (ADHD; Challman and Lipsky, 2000; Swanson and Volkow, 2002). Approximately 5–15% of children and adolescents in the U.S. are treated with MPH (Barbarelli, Katusic, Colligan, Oankratz, Weber, Mrazek, and Jacobsen, 2002), and because ADHD often continues into adulthood, many of these individuals continue to take MPH later in life (Himelstein and Halperin, 2000). MPH has been found to have abuse potential in both human and nonhuman animals (Kollins, MacDonald, and Rush, 2001), and many children prescribed MPH for ADHD have been asked to sell, trade, or give their medication to other children who do not have ADHD (Kollins et al., 2001). MPH has been found to be a

reinforcer for children diagnosed with ADHD, as they prefer to take MPH over placebo (Fredericks and Kollins, 2005). Therefore, MPH use and abuse is a valid health concern.

Despite its abuse potential, MPH has not been studied as extensively as other abused stimulants; however, multiple studies provide support for MPH as a reinforcer for rats. Collins, Weeks, Cooper, Good, and Russell (1984) found that MPH was as reinforcing as cocaine in rats by using a rating scale that took into account the amount of drug administered in relation to the drug vehicle. In another experiment, rats that self-administered amphetamine (0.06 mg/kg/infusion) continued to lever press at the same rate when the drug was switched to MPH (0.2 or 0.4 mg/kg/infusion; Nielsen, Duda, Mokler, and Moore, 1984). Additionally, previous experiments have shown that rats will self-administer a variety of doses of MPH on fixed ratio (FR) and progressive ratio (PR) schedules (Botly, Burton, Rizos, and Fletcher, 2008). Recent research demonstrated that rats lever press more for a variety of MPH doses compared to saline and lever press more on an active (drug delivery) lever than an inactive (no drug delivery) lever for MPH (Botly et al., 2008; Marusich and Bardo, 2009).

Drug reinforcement is demonstrated when behavior occurs because of the contingency to earn the drug and not for any other reason (Meisch, 1987). In order to demonstrate that subjects are engaging in the target response because of the contingency to obtain drug, at least 5 criteria need to be met. The first is that responding is no longer maintained when the drug vehicle is substituted for the drug. The second criterion is that subjects engage in more behavior on an active lever compared to an inactive lever. Third, drug self-administration must be maintained on intermittent schedules of reinforcement. Fourth, behavior needs to be differentially affected by self-administration of different doses of the drug. The final criterion is that non-contingent drug presentation does not maintain responding (Meisch, 1987). All of these criteria, except the final one, have been addressed for MPH by previous research (Botly et al., 2008; Marusich and Bardo, 2009) and have provided evidence that MPH is a reinforcer for rats.

In addition to establishing fully that MPH is a reinforcer, it is important to determine if MPH self-administration also leads to the dysfunctional pattern of intake typical of other drugs of abuse. That is, a prominent feature of drug abuse is the increase in the amount of drug used over time (DSM-IV; American Psychiatric Association, 2000). While many studies examining drug self-administration in rats limit drug access to 1-hr daily sessions, humans often take drugs over the course of longer time periods, thus making studies of long access (LgA) to drug self-administration more relevant to human drug use (Koob and Kreek, 2007). When humans are given extended access to drugs, this can lead to increased drug use (Gawin and Ellinwood, 1989).

Numerous studies have examined self-administration of stimulant drugs during long daily sessions in rats. Rats given access to i.v. cocaine during 6-hr sessions for a prolonged time show an increase in cocaine intake over time compared to rats exposed to 1–2 hr sessions (Ahmed and Koob, 1998, 1999; Mantsch, Yuferov, Mathieu-Kia, Ho, and Kreek, 2004; Oleson and Roberts, 2009; Wee, Specio, and Koob, 2007). Escalating drug self-administration has also been found for rats self-administering methamphetamine (Kitamura, Wee, Specio, Koob, and Pulvirenti, 2006; Wee, Wang, Woolverton, Pulvirenti, and Koob, 2007), heroin (Ahmed, Walker, and Koob, 2000), and d-amphetamine (Gipson and Bardo, 2009). This increase in drug self-administration during LgA sessions is often viewed as a loss of control or dysregulated drug use that characterizes the process of addiction (Koob and Le Moal, 1997). The rate at which escalation of self-administration develops, or the amount of escalation that develops, may depend on the unit dose evaluated (Gipson and Bardo, 2009; Kitamura et al., 2006; Mantsch et al., 2004). Despite the numerous studies that

have examined escalated drug self-administration during LgA sessions, no research has been published on dose-dependent MPH self-administration during LgA sessions. Thus, in addition to determining if MPH self-administration depends on contingent delivery of MPH, the purpose of these experiments was to determine if escalation of intake occurs with long access.

EXPERIMENT 1

PR schedules can be used to evaluate the reinforcing effect of a drug by establishing the breakpoint (Arnold and Roberts, 1997). Responding on PR schedules is more sensitive to dose-dependent changes in the reinforcing effect of a drug than other schedules of reinforcement (Roberts and Richardson, 1992). The reinforcing effects of many drugs of abuse have been evaluated with PR schedules including cocaine and heroin (see Stafford, LeSage, and Glowa, 1998, and Richardson and Roberts, 1996 for reviews). Since there has only been one report of MPH reinforcement using a PR schedule in rats (Botly et al., 2008), a PR schedule was used initially to determine the dose of MPH that engenders maximal responding in our laboratory.

Method

Subjects—Subjects were ten 78-day-old male Sprague-Dawley rats (Harlan Industries, Indianapolis, IN). All subjects were experimentally and drug naïve at the beginning of the experiment, and weighed an average of 283 g. Subjects were housed in individual, hanging plastic home cages, and were housed in a colony on a 16/8 hr light/dark cycle (lights on at 6:00 am). Subjects had free access to water in the home cage, and were fed 20 g of food immediately after the session. Experimental protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Kentucky, and followed the principles of laboratory animal care.

Apparatus—Experimental sessions were conducted in operant chambers for rats (28 cm × 24 cm × 25 cm; ENV-001; MED Associates, St. Albans, VT) that were housed inside sound-attenuating chambers (ENV-018M; MED Associates). Side walls were made of Plexiglas, the front and back walls were aluminum, and floors consisted of metal rods. Retractable levers (4.5 cm) were located 6 cm above the floor on each side of the food tray on the front wall, and white stimulus lights (28 V; 3 cm in diameter) were located 3 cm above each lever. A fan located in the sound-attenuating chamber produced noise to mask extraneous sounds. Experimental events were arranged and recorded by MED-PC software (Med-Associates) on a computer in the experimental room.

Procedures

Acquisition of MPH self-administration: Rats were surgically implanted with a chronic indwelling jugular catheter (0.2 mm in diameter), with one end of the catheter inserted into the jugular vein. The other end of the catheter was attached to a metal cannula that exited the skin, and was secured in a head mount adhered to the skull with dental acrylic and metal jeweler's screws. Prior to the procedure, rats were anesthetized with 80 mg/kg ketamine (i.p.) and 5 mg/kg diazepam (i.p.). Catheter patency was maintained by daily 0.2 ml infusions of a mixture containing 20 ml saline, 0.6 ml heparin, and 0.2 ml gentamicin. During experimental sessions, the cannula was attached to tubing within a flexible, spring covered leash (PHM-120; MED Associates) that was connected to a swivel (PHM-115; MED Associates) outside the operant chamber. The tubing exited the operant chamber and was connected to an infusion pump (PHM-100; MED Associates) adjacent to the sound-attenuating chamber.

Subjects were then trained to press a lever for 0.3 mg/kg/infusion MPH through the method of autoshaping (Carroll and Lac, 1993). During autoshaping sessions, the active (drug) lever was extended into the chamber on a random time 60-s schedule. The side of the operant chamber that corresponded to the active lever was counter balanced across subjects. Following 15 s of extension or immediately after a lever press, the lever retracted and an infusion (0.1 ml) of MPH was delivered over 5.9 s. The infusion was paired with a 20-s timeout signaled by the illumination of both stimulus lights. The inactive lever (no drug) was present at all times except during timeouts. Autoshaping sessions delivered ten infusions of MPH during 15 min. Subjects then remained in the chamber for 45 min with only the inactive lever present and no drug infusions available. Autoshaping sessions were paired with a subsequent session in which MPH (0.3 mg/kg/infusion) was available contingently on an FR 1 for 60 min; these sessions were separated by 30 min. Subjects were exposed to autoshaping sessions and paired FR 1 sessions for 5 consecutive days. One subject did not acquire lever pressing following this regimen and therefore was trained through an autoshaping procedure for food (Brown and Jenkins, 1968) for 3 days. Following autoshaping, subjects were given access to MPH (0.3 mg/kg/infusion) on an FR 1 schedule for three consecutive days, followed by three days on FR 2, three days on FR 3, three days on FR 4, and three days on FR 5.

MPH self-administration on a PR schedule: Subjects were then given access to MPH (0.3 mg/kg/infusion) on a PR schedule during daily 3-hr sessions. MPH was available on one lever (active lever). Responses were recorded on the other lever (inactive lever), but had no programmed consequence. The PR schedule increased the response requirement for MPH following each infusion according to an exponential scale (1, 2, 4, 6, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, etc; Richardson and Roberts, 1991). Each 0.1 ml infusion was followed by a 20-s timeout signaled by the illumination of both stimulus lights. Breakpoint, defined as the final ratio completed within the 3-hr session, was measured for each session. Subjects were exposed to 0.3 mg/kg/infusion MPH on the PR schedule for 19 sessions, except one subject that was only exposed to the PR schedule for 14 sessions due to starting the experiment 5 days later than other subjects.

Dose-effect determination: During the next phase of the experiment, subjects were given access to different doses of MPH for self-administration on the PR schedule. Subjects were tested with 0.056, 0.1, 0.56, and 1.0 mg/kg/infusion MPH in a semi-random order, with each subject tested with each dose in a different order; each dose was tested for three consecutive sessions. All subjects were then exposed to saline for self-administration on the PR schedule for three consecutive sessions.

Drug: MPH HCl (Mallinckrodt, St Louis, MO) was prepared in sterile 0.9% NaCl (saline).

Data Analysis: One subject was removed from the experiment during dose-effect determination due to catheter malfunction. A one-way repeated measures analysis of variance (ANOVA) was used to compare the average number of active lever presses across the different FR values. Linear trend analyses were used to examine stability in breakpoints and infusions earned across sessions. These tests were also used to determine when behavior was stable, and therefore ready to begin dose-effect assessment. These analyses fit a straight line to the mean breakpoint, and mean number of infusions earned across the 19 sessions of self-administration of the training dose. A linear trend analysis was used to compare the linear fit of the slopes across groups to a slope of zero. A slope that was not significantly different from zero indicated stability of self-administration. During dose-effect determination, only the final two sessions of exposure to each dose were used in graphical and statistical analyses. Another one-way repeated measures ANOVA was used to compare the average number of infusions earned at each dose of MPH (including saline) from the

dose-effect determination phase. Bonferroni-corrected paired samples *t*-tests were used as post-hoc tests to compare the number of infusions earned at each dose of MPH to the number of saline infusions earned and to compare the number of infusions earned across MPH doses. Linear and quadratic post hoc trend analyses were conducted to examine the shape of the curve. All tests were considered significant at $p < .05$, except Bonferroni-corrected *t*-tests were considered significant at $p < .01$.

It should be noted that during the 3-hr sessions, some responding occurred during the final 60 min of the session. Therefore, breakpoints illustrated in the present experiment do not necessarily represent the true breakpoints at which subjects stopped responding completely, but instead simply refer to the final ratio value completed.

Results & Discussion

Figure 1 shows the mean number of active and inactive lever presses during acquisition of self-administration of 0.3 mg/kg/infusion MPH during the incremental FR sessions. Subjects began responding for MPH on the first day of exposure, and continued to increase the number of active lever presses on the FR 1 schedule after autoshaping sessions were discontinued. As the FR value increased, the number of active lever presses increased [$F(4, 36) = 37.15, p < .01$]. When shifted to the PR schedule for a minimum of 14 sessions of self-administration of 0.3 mg/kg/infusion MPH, breakpoints stabilized for each subject such that there was less than 25% variability in the mean breakpoint across the last five sessions (results not shown). A linear trend analysis of those results revealed no significant change in either breakpoint or the number of infusions earned across sessions, indicating that responding was stable across this phase [Breakpoint: $t(1, 166) = 0.90; p > .05$; Infusions: $t(1, 166) = 0.20; p > .05$].

Figure 2 shows the number of infusions earned and the breakpoint for each unit dose of MPH and saline. Subjects earned significantly more infusions of each dose of MPH compared to saline [0.056 MPH: $t(35) = 3.80, p < .01$; 0.1 MPH: $t(35) = 6.91, p < .01$; 0.3 MPH: $t(37) = 6.17, p < .01$; 0.56 MPH: $t(37) = 7.04, p < .01$; 1.0 MPH: $t(35) = 6.17, p < .01$], and also had higher breakpoints for each dose compared to saline. A unit dose of 0.56 mg/kg/infusion MPH produced the highest breakpoint. Subjects earned significantly more infusions of 0.56 mg/kg/infusion MPH than any other dose [0.056 MPH: $t(37) = 4.31, p < .05$; 0.1 MPH: $t(37) = 3.75, p < .05$; 0.3 MPH: $t(39) = 3.06, p < .05$; 1.0 MPH: $t(37) = 2.67, p < .05$]. An overall ANOVA showed a significant difference in number of infusions earned across the different doses of MPH [$F(5, 40) = 15.45, p < .01$], and subsequent linear and quadratic post hoc trend analyses showed that the curve had a significant linear [$t(8) = 5.39, p < .01$] and quadratic [$t(8) = 4.05, p < .01$] trend. Thus, these results show that rats will self-administer varying doses of MPH on a PR schedule of reinforcement, which is consistent with a previous report (Botly et al., 2008).

EXPERIMENT 2

Experiment 1 showed that rats can be trained to self-administer MPH without any prior training to lever press for food or another drug. Additionally, Experiment 1 revealed that a unit dose of 0.56 mg/kg/infusion MPH produced the most responding when different doses of MPH were available on a PR schedule. Thus, a unit dose of 0.56 mg/kg/infusion was used in Experiment 2 to determine if there are differences in responding with contingent and non-contingent MPH on an FR schedule of reinforcement.

Method

Subjects—Subjects were eight five-month-old male Sprague-Dawley rats (Harlan Industries, Indianapolis, IN). Subjects had previous experience lever pressing for food and MPH. Subjects were housed and maintained as in Experiment 1, and weighed an average of 378 g at the beginning of the experiment. Older subjects were used in this experiment because these subjects were part of a previous experiment (see Marusich and Bardo, 2009).

Apparatus—The apparatus was the same as that used in Experiment 1.

Procedures

Contingent MPH self-administration: Rats were surgically implanted with an intravenous catheter in the jugular vein as described in Experiment 1. Subjects were exposed to contingent MPH self-administration (0.56 mg/kg/infusion, 0.1 ml volume) on a FR 5 schedule of reinforcement during 60-min daily sessions. Both levers were extended into the chamber, and no lights were illuminated. Presses on one lever (active lever) produced drug infusions and presses on the other lever (inactive lever) were recorded but had no programmed consequence. The side of the operant chamber that corresponded to the active lever was counter balanced across subjects. After an active lever press, MPH was infused over 5.9 s, followed by a 20-s time out signaled by the illumination of both stimulus lights. Lever pressing on either lever during the time out had no programmed consequence. Subjects were exposed to the contingent phase for eleven consecutive sessions, which provided ample time for response rates to stabilize. At this point, the number of infusions earned for each subject during the last five sessions was within 20% of the mean number of infusions earned for those five sessions.

Non-contingent MPH administration: In this phase, subjects were exposed to non-contingent MPH infusions given at the same rate as when they previously self-administered MPH contingently. Therefore, subjects were yoked to their own previous rate and number of MPH infusions. For non-contingent administration sessions, the mean number of infusions earned in each 5-min bin during contingent MPH self-administration was calculated for each subject during the last three days of contingent MPH administration. Non-contingent infusion sessions presented the same number of infusions per 5-min bin for each subject, with infusions distributed randomly in time within the 5-min bins. This method ensured that subjects received approximately the same amount of drug that they earned when the drug was contingent, and at the same time within the session. Sessions were made less predictable by random distribution of infusions within the 5 min bins, which made each session different from the previous session. Lever pressing during this phase had no programmed consequence, but sessions were otherwise identical to contingent sessions. MPH infusions were followed by a 20-s time out signaled by the illumination of both stimulus lights. Subjects were exposed to this condition for eleven consecutive sessions.

Drug: The drug was the same as that used in Experiment 1.

Data Analysis: A 2×11 (contingency $\times$ session) repeated measures ANOVA was used to compare lever pressing across all sessions of contingent and non-contingent MPH administration. In addition, paired sample t-tests were used to compare the number of active lever presses during the last three sessions of contingent and last three sessions of non-contingent MPH administration phases. An additional paired sample t-test was used to compare active lever presses during the final session of contingent MPH administration to the first session of non-contingent MPH administration. All statistical tests were considered significant at $p < .05$.

Results & Discussion

An ANOVA comparing data from the contingent and non-contingent phase showed a significant effect of contingency [$F(1, 7) = 42.79, p < .01$], session [$F(10, 70) = 10.10, p < .01$], and a significant interaction [$F(1, 7) = 8.78, p < .01$]. Figure 3 shows the number of active lever presses, inactive lever presses, and number of infusions of MPH during contingent and non-contingent MPH administration phases. Active lever pressing remained relatively stable across sessions during contingent self-administration (mean during last 3 sessions = 47.21 ± 1.07), while inactive lever pressing was at a low rate. When subjects were switched from contingent to non-contingent MPH administration, there was a significant increase in active lever presses [$t(7) = 2.71, p < .05$] initially. This increase may reflect an extinction burst because lever pressing no longer produced drug administration. By the end of the non-contingent phase, presses on the previously active lever decreased (mean during last 3 sessions = 11.17 ± 2.26). A comparison of the number of active lever presses across the last three days from the contingent phase and the last three days from the non-contingent phase showed that lever pressing during the two phases was significantly different [$t(46) = 11.98, p < .01$].

These results show that responding was maintained by contingent MPH self-administration. When the drug was delivered independent of responding (non-contingently), responding extinguished. This indicates that the ability of MPH to maintain responding on the active lever was not the result of a direct response-enhancing effect of MPH, which corroborates previous evidence that MPH is a reinforcer for rats.

EXPERIMENT 3

Experiment 1 found that peak responding on a PR schedule occurred at a unit dose of 0.56 mg/kg/infusion MPH, and Experiment 2 found that non-contingent delivery of this unit dose of MPH lead to a decrease in responding compared to contingent delivery. The purpose of Experiment 3 was to examine self-administration of MPH during LgA sessions; however, for Experiment 3, the unit dose of MPH was lowered (0.1 or 0.3 mg/kg/infusion), as prior research on stimulant self-administration during LgA sessions has found that escalation of drug intake tends to be more pronounced with lower doses (Gipson and Bardo, 2009; Kitamura et al., 2006).

Method

Subjects—Subjects were 30 male Sprague-Dawley rats (Harlan Industries, Indianapolis, IN) approximately 80 days old. All subjects were experimentally and drug naïve at the beginning of the experiment, and weighed an average of 289 g. Subjects were housed and maintained as in Experiment 1.

Apparatus—The apparatus was the same as that used in Experiment 1.

Procedures

Acquisition of MPH self-administration: Rats were surgically implanted with an intravenous catheter in the jugular vein as described in Experiment 1. Subjects were divided into two equal groups based on the training dose of MPH used (0.1 or 0.3 mg/kg/infusion). Subjects were trained to press the lever for their assigned dose of MPH through the method of autoshaping for seven consecutive sessions (Carroll and Lac, 1993), as described in Experiment 1. All subjects acquired lever pressing through this method using 1-hr sessions.

ShA and LgA sessions for MPH self-administration: Subjects within each dose group then were randomly divided into two groups, each of which had a different session duration.

Short access (ShA) rats continued on 1-hr daily sessions, and LgA rats shifted to 6-hr daily sessions; MPH was available on an FR 1 schedule for both groups. This produced four groups of rats: ShA 0.1; ShA 0.3; LgA 0.1; and LgA 0.3. Each ShA group began with 6 rats and each LgA group began with 9 rats. Subjects were exposed to 1-hr or 6-hr daily sessions for 21 consecutive sessions. If a subject's catheter malfunctioned, the subject was removed from the experiment and all data from these subjects were excluded in the final analysis. The number of rats that completed the experiment in each group was: ShA 0.1 $n=5$; ShA 0.3 $n=5$; LgA 0.1 $n=7$; and LgA 0.3 $n=6$.

Drug: The drug was the same as that used in Experiment 1.

Data Analysis: An omnibus $2 \times 2 \times 2 \times 12$ (session duration $\times$ dose $\times$ session $\times$ 5-min bin) ANOVA was used to identify overall effects of session duration, time within session, and dose. To further examine the effects of session duration and dose, linear trend analyses were used to examine escalating trends in self-administration across the 21 sessions in Experiment 3. These analyses fit a straight line to the mean number of infusions earned for each group across the 21 daily sessions. A linear trend analysis was used to compare the linear fit of the slopes across groups to a slope of zero. A slope that was significantly different from zero indicated escalation of self-administration. To further examine the within-session time course data, the number of infusions earned within the first 60 min of session 1 and session 21 were analyzed using a 2×12 (session $\times$ 5-min bin) repeated measures ANOVA for each dose. All tests were considered significant at $p < .05$.

Results & Discussion

An omnibus ANOVA comparing all groups showed a significant effect of session duration [$F(1, 19) = 8.84$; $p < .01$], dose [$F(1, 19) = 19.17$; $p < .01$], day [$F(1, 19) = 9.65$; $p < .01$], and time within session [$F(11, 209) = 53.11$; $p < .01$], as well as significant interactions between dose and day [$F(1, 19) = 7.35$; $p < .05$], dose and time within session [$F(11, 209) = 2.28$; $p < .05$], and time within session and session duration [$F(11, 209) = 2.27$; $p < .05$]. Figure 4a shows the mean number of MPH infusions earned for subjects in the 0.1 MPH ShA and 0.1 MPH LgA groups across the 21 sessions, and Figure 4b shows the number of MPH infusions earned for subjects in the 0.3 MPH ShA and 0.3 MPH LgA groups. To further investigate the effect of day, a linear trend analysis was conducted to examine increases in MPH intake across days. The linear trend analysis showed that the slope of the lines for the 0.1 MPH ShA and 0.3 MPH ShA groups were not significantly different from zero [0.1 MPH: $t(1, 103) = 1.81$; $p > .05$; 0.3 MPH: $t(1, 103) = 1.88$; $p > .05$], whereas the slope of the lines for the 0.1 MPH LgA and 0.3 MPH LgA were significantly different from zero [0.1 MPH: $t(1, 145) = 6.22$; $p < .05$; 0.3 MPH: $t(1, 124) = 4.30$; $p < .05$]. A comparison of both LgA groups also showed that the slopes were significantly different for the two doses [$t(1, 269) = 4.25$; $p < .05$], with the slope being greater for 0.1 than for 0.3 mg/kg/infusion MPH. These results indicate that subjects in both LgA groups self-administered more MPH over the course of the 21 sessions, with this escalation being more pronounced at a low unit dose. Subjects in both ShA groups did not show an increase in MPH self-administration across the 21 sessions.

Figures 5a–5d show the number of MPH infusions earned during each 5-min bin within the first 60 min of sessions 1 and 21 for the 0.1 MPH LgA, 0.1 MPH ShA, 0.3 MPH LgA, and 0.3 MPH ShA groups, respectively. A repeated measures ANOVA showed a significant effect of session and time in the difference between the pattern of MPH intake during the first 60 min of session 1, and the first 60 min of session 21 for the 0.1 MPH LgA group [Session: $F(1, 6) = 7.86$; $p < .05$; Time: $F(11, 66) = 13.34$; $p < .05$]. Effects of time were significant for all other groups [0.1 ShA: Time: $F(11, 44) = 15.48$; $p < .05$; 0.3 LgA: Time:

$F(11, 55) = 25.42; p < .05$; 0.3 ShA: Time: $F(11, 44) = 15.48; p < .05$], but effects of session were not significant. The significant effects of time for all groups indicates that subjects in all groups earned more MPH during the first 5–10 min of the first hr compared to later in the first hr, which may represent a loading effect. Overall, the time-dependent number of MPH infusions earned within the first hr of the session increased over the course of the 21 sessions for subjects in the 0.1 MPH LgA group, but not for subjects in any other group. Thus, although escalation of responding was observed in both LgA groups across the 6-hr session, the number of infusions earned within the first 60 min of the session only changed significantly for subjects self-administering the lower unit dose of MPH (0.1 mg/kg/infusion).

General Discussion

The results of the present experiments confirm that MPH is an i.v. reinforcer for rats. Experiments 1 and 3 found that rats will acquire self-administration of MPH without any previous lever press training for food or another drug. Results of Experiment 1 also show that rats will self-administer MPH on a PR schedule of reinforcement and will perform over 300 lever presses for one infusion of 0.56 mg/kg/infusion MPH. Rats self-administered more MPH (0.056–1.0 mg/kg/infusion) than saline. Experiment 2 also found that rats will lever press significantly more for contingent MPH self-administration compared to non-contingent MPH. Experiment 3 further demonstrated that rats given LgA to MPH self-administration will escalate MPH intake, indicating that MPH self-administration is subject to dysregulation.

Previous research has shown that rats respond for MPH across a wide range of doses on either FR and PR schedules of reinforcement, and that rats will self-administer more MPH than saline (Botly et al., 2008; Collins et al., 1984; Marusich and Bardo, 2009; Nielsen et al., 1984). The results of the present experiments extend this literature by showing that non-contingent MPH administration did not sustain lever pressing, similar to that found when contingent nicotine or cocaine is switched to non-contingent administration (Donny, Caggiula, Mielkem, Jacobs, Rose, and Sved, 1998; Pickens and Thompson, 1968). This suggests that rats are lever pressing because of the contingency for the drug and not because of some direct effect of the drug that leads to a nonspecific increase in ongoing behavior (Meisch and Lemaire, 1993). Thus, combined with results from previous research (Botly et al., 2008; Marusich and Bardo, 2009), all the criteria needed to demonstrate that subjects are lever pressing because of the contingency to obtain MPH have been met (Meisch, 1987).

The present experiments also demonstrate that rats learn to lever press for MPH without any history of lever pressing reinforced by food or a related stimulant drug (e.g. amphetamine). Previous research on MPH self-administration has been conducted by training rats to lever press for food or another drug prior to lever pressing for MPH (Botly et al., 2008; Collins et al., 1984; Marusich and Bardo, 2009; Nielsen et al., 1984). Additionally, experiments that have examined MPH self-administration in non-human primates have typically trained subjects to lever press for cocaine prior to substitution with MPH (Bergman, Madras, Johnson, and Spealman, 1989; Gasior, Bergman, Kallman, and Paronis, 2005; Johanson and Schuster, 1975; Lile, Wang, Woolverton, France, Gregg, Davies, and Nader, 2003). Therefore, the current demonstration that rats will self-administer MPH without prior training to lever press for food or another drug provides additional evidence that MPH is a reinforcer for rats.

When rats were switched to LgA (6-hr) sessions for MPH self-administration in Experiment 3, there was an escalation of drug intake across sessions compared to rats that were exposed to ShA (1-hr) sessions only. This finding is in accord with previous research on rats given long access to cocaine (Ahmed and Koob, 1998, 1999; Mantsch et al., 2004; Oleson and

Roberts, 2009; Wee et al., 2007a), amphetamine (Gipson and Bardo, 2009), or methamphetamine (Kitamura et al., 2006; Wee et al., 2007b). The present experiment also found that escalation of drug intake is more pronounced when a lower dose of MPH is self-administered, a finding consistent with previous escalation studies using amphetamine (Gipson and Bardo, 2009), cocaine (Wee et al., 2007a) or methamphetamine (Kitamura et al., 2006); however, one report found the opposite for cocaine (Mantsch et al., 2004). An additional interesting finding in the present study was that LgA rats given the lower dose (0.1 mg/kg/infusion) of MPH showed a different pattern of intake during the initial first hour across the 21 sessions, whereas the pattern of intake during this time period did not change for LgA rats given the higher dose of MPH (0.3 mg/kg/infusion). Similar results were found with d-amphetamine (Gipson and Bardo, 2009) and cocaine (Wee et al., 2007a), suggesting that the accelerated intake of low stimulant doses observed early in a LgA session is not unique to MPH.

In humans, methylphenidate is used illicitly through multiple routes of administration including intranasal, intravenous, and oral (Sussman, Pentz, Spruijt-Metz, and Miller 2006; Teter, McCabe, LaGrange, Cranford, and Boyd, 2006), with intranasal (White, Becker-Blease, and Grace-Bishop, 2006) and oral (Teter et al., 2006) being the most common. While intravenous use is not the most common route in humans, it is still a widely reported route of self-administration (Sussman et al., 2006; Teter et al., 2006), thus making the results of the present preclinical study relevant to humans. Additionally, animal models of drug abuse have been shown to have high validity when assessing the abuse potential of drugs or the reinforcing efficacy of drugs (Brady, 1991; Haney and Spealman, 2008). Given the widespread clinical use of MPH to treat ADHD, and given that MPH is a reinforcer in humans (Fredericks and Kollins, 2005), these results suggest that caution should be used when prescribing MPH to children and adolescents on a long-term basis because it is possible that MPH will be used illicitly by the individual it is prescribed for, or by other individuals it is sold or traded to.

While the present experiments contribute to the literature on MPH as an i.v. reinforcer for rats, limitations remain. No experiments presented here included a manipulation to determine if rats are lever pressing for the stimulus light rather than MPH, which has been shown to be important for nicotine self-administration (Donny, Chaudhri, Caggiula, Evans-Martin, Booth, Gharib, Clements, and Sved, 2003). Additionally, to provide further evidence that MPH is a reinforcer, these studies should be repeated with rats that are not food restricted.

In summary, the present experiments provide additional confirmatory evidence that MPH serves as an i.v. reinforcer for rats. Rats acquired lever pressing for MPH without any prior lever press training, and lever pressed over 300 times for one infusion of MPH on a PR schedule. The switch from contingent to non-contingent MPH self-administration decreased lever pressing, and rats given LgA sessions for MPH self-administration showed escalation of drug intake across sessions. Thus, MPH may be subject to abuse when available on a long-term basis, similar to that for cocaine and methamphetamine.

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Figure 1.

Number of active and inactive lever presses for the group mean plotted as a function of FR session during acquisition of MPH self-administration for Experiment 1. During the first five sessions, data are plotted from the FR 1 session only, and not from the autoshaping session.

Figure 2.
Number of infusions earned and breakpoints plotted as a function of MPH dose (log scale) for the group mean for Experiment 1. “S” stands for saline vehicle.

Figure 3.

Number of lever presses (active and inactive) and infusions earned plotted as a function of session for the group mean during contingent and non-contingent MPH administration for Experiment 2.

4b

Figure 4.

a. Number of MPH infusions earned plotted as a function of session for the 0.1 MPH ShA and LgA group means for Experiment 3. Fit lines display the best fit straight line.

b. Number of MPH infusions earned plotted as a function of session for the 0.3 MPH ShA and LgA group means for Experiment 3. Fit lines display the best fit straight line.

5a

5b

5c

Figure 5.

- Number of MPH infusions earned plotted for each 5-min bin within the first 60 min during sessions 1 and 21 for the 0.1 MPH LgA Group.
- Number of MPH infusions earned plotted for each 5-min bin within the first 60 min during sessions 1 and 21 for the 0.1 MPH ShA Group.
- Number of MPH infusions earned plotted for each 5-min bin within the first 60 min during sessions 1 and 21 for the 0.3 MPH LgA Group.
- Number of MPH infusions earned plotted for each 5-min bin within the first 60 min during sessions 1 and 21 for the 0.3 MPH ShA Group.