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Cue Effects on Methylphenidate Self-Administration in Rats

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Abstract

Associations between drugs and the stimuli paired with drugs have been proposed as primary factors in drug addiction and relapse. Previous research has found cues paired with drug infusions are important for many classes of drugs. The purpose of the present experiment was to determine if a cue light was necessary to engender reliable self-administration of methylphenidate (MPH), which is a widely prescribed drug for Attention Deficit Hyperactivity Disorder. Rats were given access to MPH (0.3 mg/kg/infusion) or saline for self-administration. Half of the rats in each group had infusions paired with a cue light, whereas the other half did not. Two additional groups of rats received MPH infusions non-contingently; one group's lever pressing turned on the cue light, and the other group's lever pressing had no consequence. Both MPH and the cue functioned as weak reinforcers on their own. The group that lever pressed for MPH paired with a cue light pressed significantly more for MPH than any other group, indicating that the cue and MPH had a synergistic effect on self-administration when combined. Taken together, these results indicate that MPH has reinforcing properties on its own, but that environmental cues also play an important role in enhancing MPH self-administration.

Keywords

methylphenidate; self-administration; environmental cues; rat

Introduction

Pavlovian associations between drugs and the stimuli paired with drugs have been proposed as primary factors in addiction and relapse (Flagel et al., 2009; Deroche-Gamonet et al., 2002). Environmental stimuli associated with drug use can come to control the same neural conditions caused by the drug, and these conditions may be similar or opposite to those caused by the drug (Deroche-Gamonet et al., 2002). Furthermore, stimulants such as nicotine enhance responding for an environmental stimulus (e.g., cue light), and this enhancement also contributes to nicotine self-administration (Donny et al., 2003). Therefore, the interaction between drug use and the cues associated with it may be bidirectional, leading to drug administration in the presence of the cues and cue seeking while under effects of the drug.

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Rats acquire cocaine and nicotine self-administration faster when the infusion is paired with a cue light (Deroche-Gamonet et al., 2002; Caggiula et al., 2002; Donny et al., 2003); in the case of nicotine, little responding is engendered in the absence of a discrete cue (Donny et al., 2003; Palmatier et al., 2006). Additionally, removal of a stimulus light previously paired with cocaine (Schenk and Partridge, 2001) or nicotine infusions (Caggiula et al., 2001) produces a decrease in self-administration. Furthermore, rats will lever press more for heroin when the infusion is paired with a light and tone combination, relative to either stimulus alone (Panlilio et al., 2000). Thus, cues paired with drug infusions can be important for many classes of drugs. One explanation of these findings is that the stimulus enhances the salience of the drug reinforcer to increase responding.

The purpose of the present experiment was to determine if a stimulus light was necessary to engender reliable self-administration of methylphenidate (MPH). MPH is currently prescribed to 5–15% of children and adolescents in the U.S. (Barbaresi et al., 2003) for the treatment of attention deficit hyperactive disorder (ADHD), and has been shown to have abuse potential in humans (Kollins et al., 2001). While MPH self-administration in rats has been demonstrated (Botly et al., 2008; Burton et al., 2010; Marusich and Bardo, 2009; Marusich et al., 2010), there has been no systematic investigation of the role of stimuli paired with MPH infusions. Given that MPH is a widely prescribed clinical treatment, it is important to examine if cue effects contribute to MPH self-administration, as such information may be important for understanding the role of non-pharmacological expectancy effects associated with prescription stimulant misuse (Looby and Earleywine, 2009). In addition, determining if MPH enhances the reinforcing effect of weak non-drug environmental stimuli may have implications for how MPH contributes to the enhancement of learning among individuals with ADHD (Advokat, 2010).

Method

Subjects

Subjects were 57–60-day-old male Sprague-Dawley rats (Harlan Industries, Indianapolis, IN) that were experimentally and drug naïve. Rats had free access to food and water in the home cage. Experimental protocols were approved by the Institutional Animal Care and Use Committee at the University of Kentucky, and followed the principles of laboratory animal care.

Apparatus

The apparatus was the same as that used in previous research (Marusich and Bardo, 2009; Marusich et al., 2010). The operant conditioning chambers were housed inside sound-attenuating chambers, with each chamber containing a house light, two retractable levers, and two white stimulus lights. Drug was delivered through a leash attached to a swivel that was connected to an infusion pump.

Procedure

Treatment groups—Rats were randomly divided into six experimental groups: (1) contingent MPH with cue (CMC; $n=12$), in which lever pressing produced MPH infusions paired with a stimulus light onset; (2) contingent MPH without cue (CM; $n=7$) that provided MPH infusions contingent upon lever pressing, with no stimulus light; (3) contingent saline with cue (CSC; $n=8$) which was identical to group CMC, except that saline was substituted for MPH; (4) contingent saline without cue (CS; $n=9$) that was identical to group CM, except that saline was substituted for MPH; (5) non-contingent MPH with cue (NMC; $n=10$) in which MPH was presented non-contingently, but lever pressing produced stimulus light onset; (6) non-contingent MPH without cue (NCM; $n=11$) in which MPH was

delivered non-contingently and lever pressing had no programmed consequence. Rats in groups NCMC and NCM were yoked to individual rats in group CMC. The mean number of infusions earned in each 5-min interval for group CMC was calculated for each rat during each session. In each session each rat in groups NCMC and NCM was presented with the same number of infusions per 5-min interval that was earned by rats in group CMC, with infusions distributed randomly in time within the 5-min intervals.

Surgical procedure—Rats were surgically implanted with a chronic indwelling jugular catheter using previously published methods (Marusich and Bardo, 2009; Marusich et al., 2010).

MPH self-administration—Autoshaping sessions were used to train rats to lever press according to assigned group conditions (Carroll and Lac, 1993; Marusich et al., 2010). For the CMC and CM groups, MPH was delivered on a random time schedule and could also be obtained by pressing the lever. Infusions were paired with lever retraction and a 20-s timeout, which was signaled by illumination of the stimulus lights for the CMC group only. CSC and CS groups were exposed to identical procedures, except that saline was substituted for MPH. Non-contingent presentation of MPH was administered in groups NCMC and NCM with infusions paired with lever retraction and a 20-s timeout, which was signaled by illumination of the stimulus lights for the NCMC group only.

Autoshaping sessions were followed by a subsequent session 30–90 min later in which MPH (0.3 mg/kg/infusion; 0.1 ml/infusion) or saline was available on an FR 1 for 60 min under assigned group conditions. Rats were exposed to autoshaping and FR 1 sessions for 7 consecutive sessions, followed by contingent sessions only as follows: 3 consecutive sessions of FR 1, then FR 2, FR 3, and FR 4, and then 7 consecutive sessions of FR 5 (cf. Marusich et al., 2011).

Data Analysis

Data were analyzed separately for the two phases of the experiment: autoshaping (days 1–7), and acquisition (FR 1–FR 5). Mixed factor analyses of variance (ANOVAs) were used to compare the number of active or inactive lever presses. Only data from the final three days of exposure to each FR value were included. Bonferroni-adjusted pairwise comparisons were used as post-hoc tests. All tests were considered significant at $p < .05$, except that alpha levels were adjusted for Bonferroni comparisons.

Results

Figure 1 shows the number of active lever presses during the autoshaping phase. Only the CMC group acquired lever pressing during the autoshaping phase. There was a significant main effect of group [$F(5, 51) = 7.22; p < .01$] and a significant session $\times$ group interaction [$F(30, 306) = 2.56; p < .01$] on active lever presses. Post hoc analyses showed that the CMC group lever pressed more than any other group. Inactive lever presses did not differ among groups (data not shown; inactive lever presses remained low across sessions, averaging less than 10 presses per session).

Figure 2 shows the number of active lever presses during exposure to each FR value after autoshaping sessions were terminated. Rats in the CMC, CM, CSC, and NCMC groups showed an increase in lever pressing as the FR value increased. The CMC group showed the most lever pressing overall. There were significant main effects of schedule [$F(4, 204) = 41.28; p < .01$] and group [$F(5, 51) = 45.15; p < .01$], and a significant group $\times$ schedule interaction [$F(20, 204) = 10.47; p < .01$] on active lever presses. Post hoc analyses showed that the CMC group lever pressed more than any other group collapsed across all FR values.

A comparison of responding on FR 5 alone revealed that the CMC group lever pressed more than any other group, and the CM group lever pressed more than the CS and NCM groups. There were no significant differences in the number of inactive lever presses (data not shown).

Discussion

There were four main findings from the current study. First, as shown previously with nicotine, contingent presentation of a cue light alone served as a weak reinforcer (cf. Donny et al., 2003). Second, a moderate unit dose of MPH (0.3 mg/kg/infusion) also served as a weak reinforcer in the absence of a contingent cue light during the infusion. Third, non-contingent delivery of this particular unit dose of MPH did not alter the reinforcing effect of the cue light. Fourth, combining contingent MPH (0.3 mg/kg/infusion) with the contingent cue light yielded a response rate greater than either reinforcer alone. Taken together, these results indicate that MPH has reinforcing properties on its own, but that environmental cues also play an important role in enhancing MPH self-administration.

Training doses are influential in acquisition of drug self-administration (Schenk and Partridge, 2000), and the effects of the cue paired with MPH infusions may depend on the training dose. Future experiments will need to be conducted to determine whether similar relationships between self-administration rates and environmental cues occur with different unit doses of MPH. Similarly, the present experiment did not address the effects of removing the cue after rats were trained to lever press with it, or address the introduction of the cue after rats were trained to lever press without it. Additionally, the FR ramping procedure (FR 1-FR 5) used in the present experiment was not identical to that used in other labs with other stimulants, and therefore may also have influenced the outcome of the present experiment.

Similar to what has been found with psychomotor stimulants cocaine and nicotine (Caggiula et al., 2002; Deroche-Gamonet et al., 2002; Donny et al., 2003), pairing a stimulus light with infusions produced faster acquisition of MPH self-administration. However, in contrast to an experiment with cocaine (Deroche-Gamonet et al., 2002), MPH self-administration was significantly reduced when infusions were not paired with a cue. Non-contingent MPH also did not increase responding for the cue light, as found previously with nicotine (compare NCMC with CSC; Donny et al., 2003). It remains to be determined whether such differences between these stimulants can be related to differences in relative unit dose of the stimulant drugs or to other experimental features that differed among the three laboratories.

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Figure 1.

Number of active lever presses for the mean of each group plotted as a function of session during acquisition of MPH self-administration. Data are plotted from the FR 1 session that followed the autoshaping session. CMC: contingent MPH with cue; CM: contingent MPH without cue; CSC: contingent saline with cue; CS: contingent saline without cue; NCMC: non-contingent MPH with cue; NCM: non-contingent MPH without cue. The asterisk denotes that the CMC group was significantly different from all other groups

Figure 2.

Number of active lever presses for the mean for each group plotted as a function of FR requirement. Asterisks denote that the CMC group was significantly different from all other groups. The pound sign denotes that the CM was significantly different from the CS and NCM groups. All other details are as in Figure 1.