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Pretreatment with methylphenidate sensitizes rats to the reinforcing effects of cocaine

Susan Schenk[a,1], Sari Izenwasser[b,*]

[a]Department of Psychology, Texas A&M University, 77843, College Station, TX, USA
[b]Department of Psychiatry and Behavioral Sciences, University of Miami School of Medicine, 1695 NW 9th Avenue (D-21), Miami, FL, USA

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Abstract

Repeated administration of cocaine produces sensitization to its locomotor-activating effects and increases the rate at which cocaine self-administration behavior is acquired. Methylphenidate is administered clinically on a daily basis, predominantly to children and adolescents, for the treatment of attention-deficit hyperactivity disorder (ADHD). It has been demonstrated previously that pretreatment with methylphenidate administered to periadolescent rats decreased the latency to acquisition of cocaine self-administration. Since methylphenidate is often also administered to adults with ADHD, the present study was conducted to determine the effects of prior administration of methylphenidate (5 or 20 mg/kg/day for 9 days) to adult rats on the rate of acquisition for cocaine self-administration (0.25 mg/kg/infusion). The higher dose of methylphenidate significantly decreased the latency for acquisition of this behavior, suggesting that the rats were sensitized to the reinforcing effects of cocaine after treatment with methylphenidate. These findings add to the growing body of evidence suggesting cross-sensitization between the behavioral effects of psychostimulants. Further, insofar as self-administration is a reliable measure of abuse liability, these data suggest that a short-duration pretreatment with a high dose of methylphenidate to adults increases vulnerability to cocaine abuse.

Keywords: Methylphenidate; Ritalin; Cocaine; Sensitization

1. Introduction

A number of studies have demonstrated that repeated intermittent exposures to various psychostimulants including cocaine (Post and Rose, 1976; Reith et al., 1987; Kalivas et al., 1988; Segal and Kuczenski, 1992) and amphetamine (Hooks et al., 1991, 1992; Patrick et al., 1991) resulted in an enhancement of some of their behavioral effects. The sensitized behavioral response that occurs following preexposure is characteristic of many drugs of abuse and has been implicated in the transition from drug use to abuse (Robinson and Berridge, 1993).

Methylphenidate is a psychostimulant that is prescribed for the treatment of attention-deficit hyperactivity disorder (ADHD) and the increase in prescribed use in recent years has led to concern of potential for abuse. This possibility has received relatively little attention in the human literature (see Kollins et al., 2001 for review), although a recent study showed that greater than 16% of students reported they had tried methylphenidate recreationally and 12.7% reported they had taken the drug intranasally (Babcock and Byrne, 2000). In addition, a small number of preclinical studies have suggested that methylphenidate is self-administered by laboratory animals (Bergman et al., 1989; Collins et al., 1984; Griffiths et al., 1975; Johanson and Schuster, 1975) and shares discriminative stimulus properties with other stimulant drugs (Colpaert et al., 1979).

Following repeated administration, some studies have reported a sensitized response to the effects of this drug (Meririnne et al., 2001; Gaytan et al., 1997; Crawford et al., 1998; Shuster et al., 1982; McDougall et al., 1999), whereas others have reported tolerance to the effects of methylphenidate (McNamara et al., 1993; Crawford et al., 1998; Izenwasser et al., 1999). These inconsistent results might

* Corresponding author. Tel.: +1-305-243-2032; fax: +1-305-243-5475.
E-mail address: s.izenwasser@miami.edu (S. Izenwasser).
[1] Current address: School of Psychology, Te Kura Maatai Hinengaro Victoria University of Wellington, PO Box 600,Wellington, New Zealand.

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be attributed to differences in time of testing, behavioral measures assessed, dose of methylphenidate administered and/or dosing regimen (Gaytan et al., 2000).

Of particular relevance to abuse potential, following repeated pairings of methylphenidate and environmental stimuli, there was a dose-dependent increase in the amount of time spent in an environment that had been associated with the drug (conditioned place preference) (Martin-Iverson et al., 1985; Meririnne et al., 2001). Further, pretreatment with methylphenidate increased the conditioned reinforcing properties of a low dose of methylphenidate as measured by place conditioning (Meririnne et al., 2001).

Other preclinical studies have examined the ability of pretreatments with one drug to alter the response to alternate drugs (cross-sensitization) (Hirabayashi et al., 1991; Kalivas and Weber, 1988; Schenk et al., 1989–1990, 1991a,b). In the case of methylphenidate, some studies have indicated that preexposure rendered animals more sensitive to the effects of amphetamine or cocaine. In one study (Segal and Kuczenski, 1999), rats were pretreated with an escalating dose regimen of methylphenidate that culminated in a series of daily "binges" of a high dose of methylphenidate (four successive daily injections of 30.0-mg/kg methylphenidate at 2-h intervals) prior to a test of the ability of a high dose of amphetamine (2.5 mg/kg) to elicit stereotyped responses. This pretreatment resulted in a sensitized response to amphetamine. In addition, repeated exposure to a lower dose of methylphenidate (1.0 mg/kg twice daily for 5 days) sensitized rats to the locomotor-activating effects of a lower dose of amphetamine (0.5 mg/kg) (Kuczenski and Segal, 2001).

Pretreatment with a low dose of methylphenidate also rendered rats more sensitive to the locomotor-activating and -reinforcing effects of cocaine (Brandon et al., 2001). In this study, the reinforcing effects of cocaine were measured by determining the latency to acquisition of low-dose cocaine self-administration. Rats that were pretreated with moderate doses of methylphenidate (5.0 or 10 mg/kg/day for 7 days) were more responsive to the motor-activating effects of cocaine. Rats exposed to a lower dose of methylphenidate (2.0 mg/kg/day) self-administered a dose of cocaine (75 μg/kg/infusion) that was too low to maintain responding for control rats when tested during this 5-day period. Since the latency to acquisition of self-administration is inversely related to the dose of cocaine that serves as the reinforcer (Schenk and Partridge, 2000; Schenk et al., 1991a,b, 1993), these data suggest that methylphenidate pretreatment sensitized rats to the reinforcing effects of cocaine and shifted the dose–effect curve for the acquisition of cocaine self-administration to the left.

The Brandon et al. (2001) study made use of adolescent rats (4–5 weeks of age) in an attempt to model the effects of methylphenidate in younger humans. The rationale for this approach was that many ADHD subjects are diagnosed and treated as children. Therefore, the examination in younger rats would more closely approximate effects in this age group. A large percentage of people diagnosed with ADHD and treated with psychostimulant medication are, however, adults (Wender et al., 2001). Thus, it is of interest to see what the effects are of methylphenidate on cocaine self-administration in adult rats. In addition, most preclinical studies that have demonstrated sensitization and cross-sensitization have used sexually mature adult rats as subjects and so the effects of repeated methylphenidate exposure on the response to other drugs of abuse can be compared to a large number of other studies that have used various protocols. This is of interest because methylphenidate has the unique profile of inhibiting dopamine and norepinephrine uptake with similar affinities to cocaine yet has very low affinity for inhibiting serotonin uptake, unlike cocaine (Pan et al., 1994).

In the present study, the acquisition of self-administration of a higher dose of cocaine (0.25 mg/kg/infusion) was measured for mature rats that received pretreatment with methylphenidate or vehicle. The higher dose of cocaine resulted in acquisition of self-administration for a large percentage of both control and methylphenidate-treated rats, thereby allowing an assessment of the magnitude of the effect of methylphenidate pretreatment on the self-administration acquisition curve.

2. Materials and methods

2.1. Subjects

Subjects were male Sprague–Dawley rats (Harlan, TX) weighing 325–350 g (approximately 12 weeks old). They were housed individually in hanging polycarbonate cages. The humidity- and temperature-controlled colony at Texas A&M University was kept on a 12:12-h lights condition with lights on at 08:00 h. Food and water were freely available except during testing. All tests were approved by the University Laboratory Animal Care Committee and principles of laboratory animal care were followed (NIH publication no. 85-23, rev. 1985). All tests were carried out during the light cycle between 10:00 and 17:00 h.

2.2. Surgery

A chronic indwelling Silastic catheter was implanted in the right jugular vein. Briefly, the rats were deeply anesthetized with ketamine (60.0 mg/kg) and pentobarbital (20.0 mg/kg). The external jugular vein was isolated, the catheter was inserted and the distal end (22-G stainless steel tubing) was passed subcutaneously to an exposed portion of the skull where it was fixed to embedded jeweler's screws with dental acrylic. Each day, the catheters were infused with 0.1 ml of a sterile saline solution containing heparin (1.25 U/ml), penicillin G Potassium (250,000 U/ml) and streptokinase (8000 IU/ml) to prevent infection and the formation of clots and fibroids. The rats were allowed 5 days

postsurgery for recovery. Sample sizes for each group are indicated in Section 2.4 and represent the number of subjects (generally 75–80%) that completed testing with patent catheter lines. Patency was confirmed by the immediate loss of the righting reflex produced by an infusion of sodium pentobarbital (15.0–20.0 mg/kg iv) following the completion of testing.

2.3. Apparatus

Self-administration testing was carried out in operant chambers (Med-Associates, ENV-001) equipped with two levers. Depression of one lever (the active lever) resulted in an intravenous infusion of cocaine HCl dissolved in sterile physiological saline and heparin (3 U/ml). Depression of the other lever (the inactive lever) was without programmed consequence. Drug delivery and data acquisition were controlled by the OPN software package (Spencer and Emmett-Oglesby, 1985). Cocaine deliveries were made via mechanical pumps (Razel Model A with 1-rpm motor equipped with 20.0-ml syringes) in a volume of 0.1 ml over 12.0 s. For all groups, the illumination of a house light located above the active lever was coincident with drug delivery.

2.4. Procedure

On each of 9 pretreatment days, rats received daily intraperitoneal injections of saline (n=18), 5.0-mg/kg methylphenidate HCl (n=17) or 20.0-mg/kg methylphenidate HCl (n=14). Each injection was in a volume of 1.0 ml/kg and was administered between 10:00 and 12:00 h. Tests of the acquisition of cocaine self-administration began 1 day following the last of the pretreatments. Acquisition of cocaine self-administration (0.25 mg/kg/infusion) was measured during 10 daily 2-h sessions. This dose of cocaine was chosen since we have found that the average number of days to acquisition of self-administration is 6–7 days. Therefore, the observation of both increases and decreases in latency to acquisition can be measured. When a higher dose of cocaine (0.5 or 1.0 mg/kg/infusion) is used in these acquisition studies, latency to acquisition is shorter and it is difficult to measure further decreases as a result of pretreatment. When a lower dose (0.125 mg/kg/infusion) of cocaine is used, the latency to acquisition of self-administration is very long and a significant number of subjects fail to acquire self-administration within a 20-day test period (Schenk and Partridge, 2000; Schenk et al., 1991a,b, 1993). Therefore, the use of the 0.25-mg/kg/infusion dose allowed efficient measurement of increases or decreases in latency to acquisition following pretreatment. On these days, the session began with an experimenter-administered priming injection of cocaine (0.25 mg/kg). Thereafter, infusions were delivered on a FR-1 schedule of reinforcement by depression of the active lever. Inactive lever responses were recorded but had no programmed consequences.

2.5. Data analysis

The number of active lever responses produced on each day of testing for the saline and each of the methylphenidate preexposure groups was compared using separate repeated-measures ANOVAs (Days×Pretreatment). The criteria for acquisition of self-administration were (1) a minimum of 30 active lever responses per session and (2) a minimum of 2:1 ratio active/inactive lever responses. Acquisition was defined as the first day that this criterion was met for 3 consecutive days. The percent of animals for the saline and each of the methylphenidate preexposure groups that acquired self-administration according to these criteria on each day was compared using the Wilcoxin Signed Ranks Test. Since some subjects from each group failed to acquire self-administration within the period tested, the median number of days to acquisition was determined and was compared using a Mann–Whitney U-test.

2.6. Drugs

Cocaine HCl (NIDA) and methylphenidate HCl (RBI, Natick, MA) were dissolved in physiological saline. Cocaine infusions were delivered in a volume of 100 μl over a period of 12 s. Methylphenidate was delivered in a volume of 1.0 ml/kg ip. All drug weights refer to the salt.

3. Results

Fig. 1 shows the number of active and inactive lever responses produced during each of 10 days of self-administration training (0.25 mg/kg/infusion) for rats that were pretreated with methylphenidate. For all groups, responding on both levers was comparable during the early days of testing. During the latter days, however, responding on the inactive lever decreased and responding on the active lever increased.

Responding of rats pretreated with saline or 5.0-mg/kg methylphenidate was comparable. A two-way repeated-measures ANOVA (Pretreatment×Day) on active lever responses revealed a significant main effect of Day [$F(9,297)=4.301$, $P<.001$]. However, the effect of Pretreatment [$F(1,33)=0.541$, not significant (NS)] or the interaction between Pretreatment and Day [$F(9,297)=1.671$, NS] was not significant. An ANOVA on the active lever responses of rats pretreated with saline or 20.0-mg/kg methylphenidate also revealed a significant main effect of Day [$F(9,270)=5.695$, $P<.001$]. In contrast to the data from rats pretreated with 5.0-mg/kg methylphenidate, however, a significant interaction between Pretreatment and Day was obtained overall [$F(9,270)=3.291$, $P<.001$]. Active lever responses of rats pretreated with 20.0-mg/kg methylphenidate were higher than those of saline-pretreated rats on Day 5, 6 and 10 ($P<.05$).

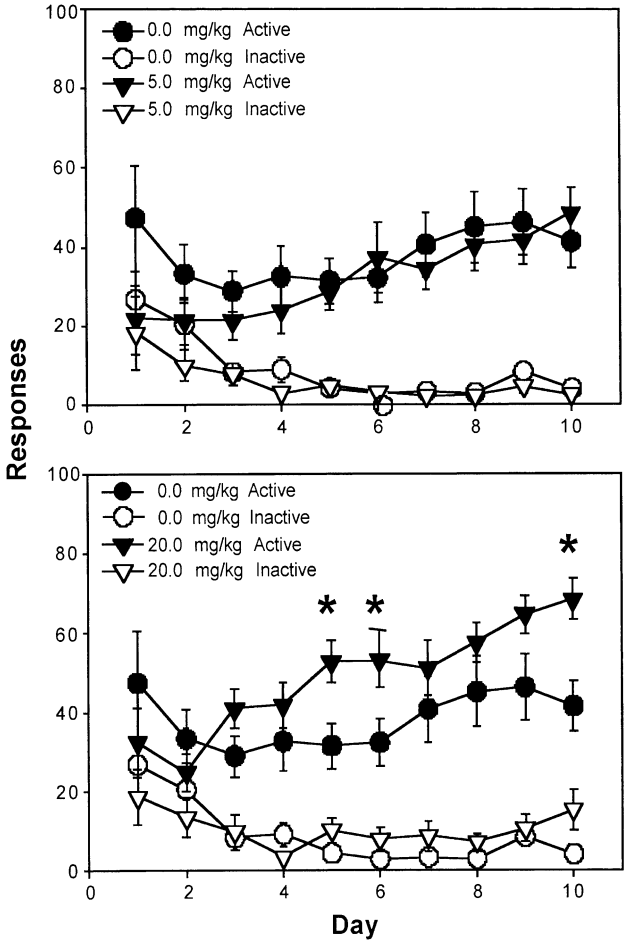

Fig. 1. Active and inactive lever responses produced during each of 10 days of self-administration training (0.25 mg/kg/infusion) for rats that were pretreated with methylphenidate for 9 days. Data comparing responding for rats pretreated with either saline or 5.0-mg/kg methylphenidate are presented in the top panel and data comparing responding for rats pretreated with either saline or 20.0-mg/kg methylphenidate are presented in the bottom panel. *P<.05 compared to saline active lever responses.

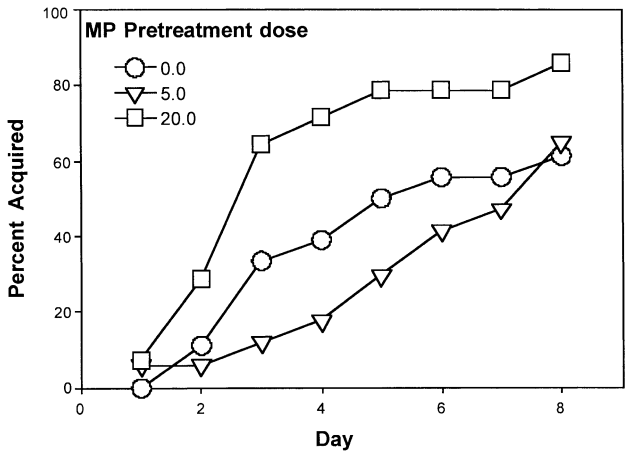

Fig. 2. Percent of rats reaching criterion for acquisition of cocaine self-administration behavior daily over an 8-day period of testing. There is a shift to the left in the curve of rats pretreated with methylphenidate (20 mg/kg/day) for 9 days prior to cocaine self-administration.

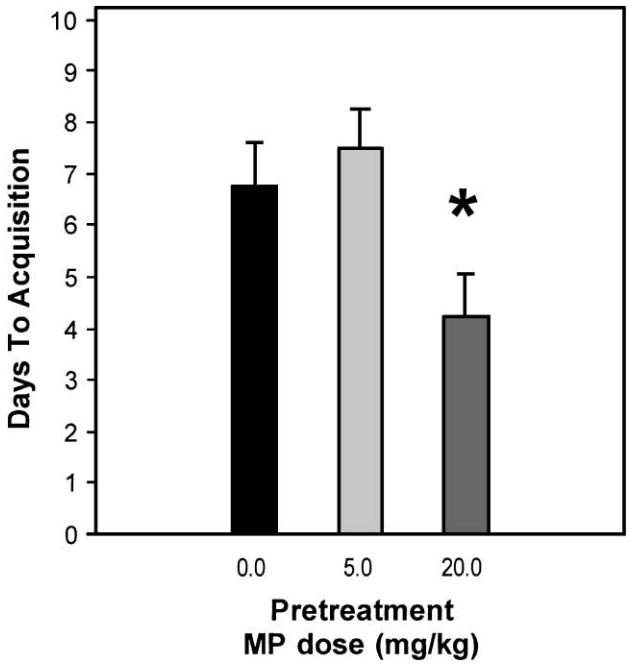

Fig. 3. Median number of days to acquisition of rats pretreated with saline or 5.0 or 20.0 mg/kg methylphenidate. Latency to acquisition of cocaine self-administration was decreased for rats that had received the pretreatment consisting of nine daily exposures to 20.0-mg/kg methylphenidate (*P < .05).

Fig. 2 shows the percent of rats that reached criterion for acquisition of cocaine self-administration by day. These data show that there is a dose-dependent shift to the left for acquisition of this behavior, with the rats treated with 20-mg/kg methylphenidate reaching criterion sooner that rats treated with saline (Wilcoxin Z=−2.812, P=.005). In contrast, the rats treated with 5-mg/kg methylphenidate were not significantly different from those treated with saline (Z=1.686, P=.09).

Fig. 3 shows the median number of days to acquisition of rats pretreated with saline or 5.0 or 20.0 mg/kg methylphenidate. Pretreatment with 5.0-mg/kg methylphenidate failed to significantly alter the latency to acquisition of cocaine self-administration. Latency to acquisition of cocaine self-administration, however, was decreased for rats that had received the pretreatment consisting of nine daily exposures to 20.0-mg/kg methylphenidate (P=.048).

4. Discussion

Following a 9-day exposure regimen, rats that were pretreated with methylphenidate acquired cocaine self-administration more rapidly than rats that were pretreated with saline. Pretreatment with the higher dose of methylphenidate increased responding on the active vs. inactive lever. Pretreatment with a lower dose of methylphenidate (5 mg/kg/day) produced no significant effect on this measure of the acquisition of cocaine self-administration.

For control rats, the acquisition of low-dose cocaine self-administration is gradual and occurs over several days (present results) (Horger et al., 1990; Schenk and Partridge, 2000; Schenk et al., 1991a,b, 1993). During initial tests, the majority of rats fail to acquire self-administration, but reliable responding becomes apparent during later tests. This protracted (delayed) development of self-administration suggests that this dose of cocaine is not initially reinforcing to many rats but becomes an effective reinforcer with repeated exposure. This contrasts with the acquisition of higher-dose self-administration that is characterized by a leftward shift in the acquisition curve, compared to the lower doses. When higher doses are available, a greater percentage of the rats acquire cocaine self-administration during the early days of testing and there is an overall decreased latency in the acquisition of cocaine self-administration (Schenk and Partridge, 2000; Schenk et al., 1991a,b, 1993). The leftward shift in the acquisition curve and the decreased latency to acquisition of low-dose cocaine self-administration following pretreatment with methylphenidate are, therefore, consistent with sensitization to the reinforcing effect of cocaine.

It is possible that following the 9-day pretreatment regimen, cocaine was more rapidly self-administered because of its ability to allay withdrawal effects. A previous study, however, showed minimal withdrawal effects after a 7-day pretreatment regimen of this dose of methylphenidate (Meririnne et al., 2001). The decreased latency to acquisition more likely reflects a direct effect on the neurochemical systems underlying cocaine reinforcement and/or more indirect alterations in neurotransmission in areas that underlie associative learning.

These data add to a growing database concerning cross-sensitization among the effects of a variety of stimulants. The pharmacological bases for the different drug effects provide some insights into relevant neurochemical changes that might underlie sensitization. In this regard, it is noteworthy that cocaine and methylphenidate have approximately equal affinities for the dopamine transporter (Deutsch and Schweri, 1994), but in contrast to cocaine, methylphenidate has a very low affinity for the serotonin transporter (Pan et al., 1994). Since methylphenidate pretreatment produces sensitization to the reinforcing effects of cocaine, the inhibition of serotonin uptake by cocaine might play a small role in the development of sensitization to its reinforcing effects produced by pretreatment with noncocaine stimulants.

Some criticisms concerning the pretreatment regimens in rats have been raised with respect to the relevance to doses administered in the treatment of ADHD. Children are generally administered maximal doses of about 0.5 mg/kg administered twice per day, which is substantially lower than the 20.0-mg/kg dose administered to the rats in the present study. Comparisons of doses for rats and humans on the basis of weight must be made cautiously since there exist differences in metabolism and pharmacokinetics between species (Wargin et al., 1983). In the present study, a dose of methylphenidate (20.0 mg/kg) administered for a short period of time (9 days) produced a sensitized response to the reinforcing effect of cocaine. A dose of 20.0-mg/kg cocaine administered for 9 days produced sensitization to its reinforcing effects (Horger et al., 1990). Methylphenidate is equipotent to cocaine in many behavioral tests and in terms of its ability to inhibit dopamine uptake (Deutsch and Schweri, 1994; Volkow et al., 1995; 1999). Dopaminergic mechanisms have been implicated in the development of sensitization to the behavioral effects of both cocaine (Henry, et al., 1998) and methylphenidate (Meririnne et al., 2001). Therefore, in the present study, we administered a dose of methylphenidate for a period of time that was expected to produce effects that were comparable to effects produced by cocaine itself. Since sensitization was produced, these data provide a set of parameters that increase the vulnerability to cocaine self-administration.

The magnitude of the effects of repeated exposure might be related to the dose administered during pretreatment and/or the pretreatment duration. For example, 9-day pretreatment with a single injection of cocaine (20.0 mg/kg/day) produced sensitization to the locomotor-activating and -reinforcing effects of subsequent cocaine injections (Horger et al., 1990), whereas a 5-day pretreatment regimen of administration of this dose of cocaine was ineffective (Schenk and Partridge, 2000). A 5-day pretreatment of two daily injections of 20.0-mg/kg cocaine, however, increased the subsequent reinforcing effects of cocaine (Schenk and Partridge, 2000). Thus, there might be a trade-off between dose and duration in that high-dose administrations administered over a short period of time might produce effects that are comparable to low-dose administrations administered over a longer period of time. Although the pretreatment parameters used in the present study vary from those used in humans for the treatment of ADHD, it is possible that treatment with lower doses over a longer period of time, as is the case in children or adults treated for ADHD, might produce comparable effects. Indeed, a recent study demonstrated a sensitized response to the reinforcing properties of cocaine following pretreatment with a lower dose of methylphenidate (2.0 mg/kg/day) to periadolescent rats (Brandon et al., 2001). In the present study, pretreatment with a higher dose of methylphenidate (5.0 mg/kg) to adult rats failed to sensitize rats to the reinforcing effects of cocaine. These discrepancies suggest that younger subjects might be particularly susceptible to the effect of methylphenidate preexposure.

Self-administration by laboratory animals is a reliable determinant of abuse potential (Johanson and Fischman, 1989). The cross-sensitization between these two drugs suggests that methylphenidate administration may predispose to cocaine use, thereby increasing the risk for subsequent abuse. A large number of treatment-seeking cocaine abusers were diagnosed with ADHD as children (Rounsaville et al., 1991), suggesting that they received medication

for the disorder. A larger percentage of adults who were treated with methylphenidate as children used cocaine when compared to untreated ADHD subjects or age-matched controls (Lambert and Hartsough., 1998; Schenk and Davidson, 1998).

In contrast to these findings, some studies have suggested that methylphenidate treatment in humans protects against substance use disorders (Biederman et al., 1997, 1999). It is important to note that subjects in these studies were receiving some sort of medication at the time of follow-up (Biederman et al., 1997). Concomitant exposure to stimulant medication might reduce other stimulant use by acting as a substitution. Indeed, it has been suggested that methylphenidate might be a candidate pharmacotherapy for cocaine abuse by acting in such a capacity (Grabowski et al., 1997). Of greater importance, the use of substances by the relatively young subjects (15–19 years of age) from the control and the ADHD groups was primarily restricted to nonstimulant drugs (Biederman et al., 1997, 1999). It has been shown that initial use of cocaine and other stimulants tends to be delayed relative to use of other drugs (Kandel and Davies, 1991; Kandel et al., 1992; Kandel and Yamaguchi, 1993). Therefore, an adequate test of the possibility that prior treatment with methylphenidate increases the vulnerability to stimulant abuse in humans would involve older subjects than reported by Biederman et al. (1997, 1999), who are not still taking stimulant medication for the treatment of ADHD. The present data suggest that methylphenidate preexposure in adulthood would be expected to increase the reinforcing effects of cocaine.

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