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# Chronic methylphenidate alters locomotor activity and dopamine transporters differently from cocaine

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**Abstract**

Continuous infusion of cocaine produces partial behavioral tolerance to its locomotor activating effects, while daily injections produce sensitization. Methylphenidate binds with a similar affinity to cocaine at the dopamine transporter, but has a much lower affinity for the serotonin transporter than does cocaine. This study was done to compare the effects of chronic methylphenidate with chronic cocaine. The pattern of locomotor activity over a 7 day treatment period was significantly different from cocaine. Methylphenidate elevated activity on each day, compared to saline, yet neither tolerance to a continuous infusion of the drug, nor sensitization to repeated daily injections was produced. We have previously shown that neither of these treatments with cocaine produces significant alterations in dopamine transporter density 1 day after the end of treatment. In contrast, methylphenidate injections significantly decreased dopamine transporters in rostral caudate putamen, with no change in nucleus accumbens. Continuous infusion of methylphenidate had no effect on dopamine transporters in either brain region. These findings provide further evidence that different classes of dopamine uptake inhibitors may interact with the dopamine transporter in qualitatively different manners. Furthermore, it is possible that the inhibition of serotonin uptake by cocaine may contribute to the adaptations in behavioral activity that are seen during chronic treatment. 

*Keywords:* Cocaine; Dopamine; Transporter; Methylphenidate

## 1. Introduction

Chronic treatment with an uptake inhibitor such as cocaine has been shown to produce long-lasting behavioral effects that persist once the drug has been stopped. Characteristically, intermittent injections of cocaine (either once or several times daily) produce a sensitization to the locomotor activating effects of the drug that is evidenced by an increased responsiveness over time to a given dose of the drug (Post and Rose, 1976; Reith et al., 1987; Kalivas et al., 1988; Segal and Kuczenski, 1992). In contrast, this sensitized effect is not seen when cocaine is administered via a continuous infusion (Reith et al., 1987; Inada et al., 1992; King et al., 1994; Kunko et al., 1998). Neither selective dopamine, norepinephrine or serotonin uptake inhibitors produces the same alterations in behavior as does cocaine (Izenwasser et al., 1999). Thus, it is possible that an interaction between two or more of these neurotransmitter systems is involved in the adaptations that occur in response to chronic cocaine administration.

Methylphenidate ($K_i = 199$) has a similar potency to cocaine ($K_i = 224$) at the dopamine transporter (Deutsch and Schweri, 1994), yet lacks its affinity for the serotonin transporter (Pan et al., 1994). Because of this characteristic, chronic treatment with this drug could provide information on the interaction between dopamine and serotonin reuptake on the behavioral effects of chronic cocaine. In addition, since methylphenidate is clinically administered on a daily basis for treatment of hyperactivity and attention deficit disorder, it was of interest to know the effects of this treatment. Previous studies have shown that methylphenidate stimulates locomotor activity (Mueller, 1993; McNamara et al., 1993; Gaytan et al., 1996), however,

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there is some controversy as to whether sensitization or tolerance develops upon chronic administration (McNamara et al., 1993; Gaytan et al., 1997a).

The present study was conducted to measure the effects of chronic methylphenidate in two different administration paradigms. The effects of a continuous infusion and of repeated daily injections of methylphenidate were measured on locomotor activity and stereotypy. These treatments produced tolerance and sensitization to cocaine on these measures. In addition, the effects of these treatments on dopamine transporter binding in the caudate putamen and nucleus accumbens (dopamine terminal regions) and the substantia nigra and ventral tegmental area (dopamine cell body regions) of rats were measured.

## 2. Materials and methods

### 2.1. Drugs

Drugs were obtained from the following sources: methylphenidate from the National Institute on Drug Abuse (Rockville, MD). [$^{125}$I]RTI-121 (approximately 2200 Ci mmol$^{-1}$) from New England Nuclear (Boston, MA).

### 2.2. Chronic drug treatment

Male Sprague–Dawley rats (200–225 g, Taconic, Germantown, NY, USA) were maintained on a 12/12 h light/dark cycle with unrestricted access to rat chow and water. For the continuous infusion experiments, animals were anesthetized with halothane, and Alzet osmotic minipumps were implanted subcutaneously between the scapulae, as previously described (Izenwasser et al., 1990; Kunko et al., 1997; Kunko et al., 1998). The pumps, model 2ML1, (Alza, Palo Alto, CA) delivered approximately 10 μl h$^{-1}$ for 7 days. Pumps contained a concentration of drug resulting in the delivery of approximately: 44 mg kg$^{-1}$ day$^{-1}$ of methylphenidate or saline (0.9% sodium chloride) as control. The dose of methylphenidate was chosen to match dopamine transporter occupancy based on the affinity of methylphenidate as compared to the cocaine dose used in our previous studies (Izenwasser and Cox, 1992; Kunko et al., 1998; Izenwasser et al., 1999). Actual doses were determined by average weight of each group of animals, and average pumping volume of the pumps. After the pumps were implanted, each rat was singly housed for the duration of the experiment. After 7 days, the animals were killed and their brains removed to an ice cold dish for dissection.

For the injection studies, rats were injected daily with either methylphenidate (44 mg kg$^{-1}$ day$^{-1}$) or saline. The total daily dose was split into two injections. The first (18 mg kg$^{-1}$) was given immediately prior to behavioral testing and the second dose (26 mg kg$^{-1}$) was administered 4 h later. The reason for this was to keep the daily dose equal to what was administered via osmotic minipump in the continuous infusion studies, while using a low enough dose for behavioral testing to protect against a ceiling effect.

### 2.3. Locomotor activity testing

Locomotor activity was measured for 1 h daily, as previously described (Kunko et al., 1998; Izenwasser et al., 1999). Rats were placed in clear acrylic chambers (16 × 16 inches) inside Digiscan activity monitors (Omnitech Electronics, Columbus, OH) that were equipped with infrared light sensitive detectors mounted 2.5 cm apart along two perpendicular walls. Mounted along the opposing walls were infrared light beams that were directed at the detectors. One count of horizontal activity was registered each time the subject interrupted two successive beams. Repetitive interruptions of the same beam due to behaviors such as grooming or head bobbing were not included in this measure, but were counted as stereotypy. Although this measure of stereotypy is not perfect, in that the type of stereotypic behavior was not observed, it does provide counts for repeated breaks of the same light beam. As such, while it is a measure of repeated movement in a single location, it does not provide a complete view of behavior. Each test session was 60 min in duration. Animals were maintained on a 12 h light/dark schedule with lights on at 7 AM and off at 7 PM. All behavioral testing was done during the light schedule between 1 and 4 PM with each group tested at the same hour each day.

Locomotor activity data were analyzed by two-way Analysis of Variance (ANOVA) with repeated measures, for each drug. Significant treatment effects were followed by post hoc analyses with Fisher's Protected Least Significant Difference (PLSD). Significant treatment by time interactions were followed by tests for simple main effects and Fisher's PLSD. $P$ values less than 0.05 were considered significant.

### 2.4. Quantitative autoradiography

At 24 h after pumps were removed, or after the last injection, the animals were killed by decapitation. Their brains were quickly removed and frozen in isopentane on dry ice, then stored at −70°C. Slices (20 μm) from the caudate putamen and nucleus accumbens, and from the substantia nigra/ventral tegmental area were thaw-mounted on gelatin/chromate-coated slides and stored at −70°C prior to assay.

For the dopamine transporter binding assay, sections were thawed to room temperature and incubated for 60 min with 0.07 nM [$^{125}$I]RTI-121 in binding buffer (137 mM NaCl, 2.7 mM KCl, 10.14 mM $Na_2HPO_4$, 1.76 mM $KH_2PO_4$ and 10 mM NaI). Sections were then washed twice in ice-cold buffer, dipped in ice-cold deionized water, and dried with a stream of cool dry air. Slides and

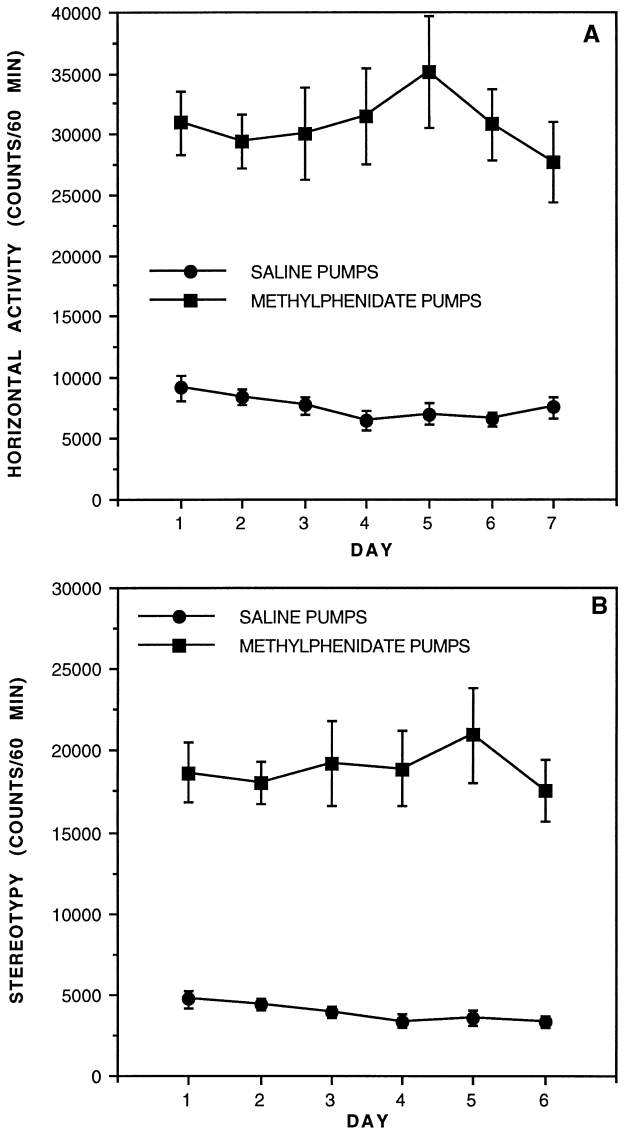


Fig. 1. Horizontal locomotor activity (A) and stereotypy counts (B) in animals treated with methylphenidate ($n = 11$) or saline ($n = 12$) via subcutaneous osmotic minipumps. Activity tests were conducted for 1 h each day, and the data are represented as counts per 60 min observation period. The tests began four hours after the pumps were implanted (day 1), and continued for a total of 7 days. Both horizontal activity and stereotypy were significantly elevated in the methylphenidate group, vs. control, on each day of testing ($P < 0.05$). Neither measure in the methylphenidate group was significantly altered over the course of the treatment period. Data are means ± S.E.M.

standards ($^{125}$I-labeled microscales, Amersham, Arlington Heights, IL) were apposed to radiosensitive film for 2 days at 4°C. Nonspecific binding was defined by the presence of 100 μM cocaine HCl.

Films were developed in Kodak GBX developer and fixative, and autoradiograms were analyzed using a Macintosh-based image analysis system (NIH, Image 1.60 software). Brain images were quantified using curves generated from the labeled standards. Data were analyzed by Analysis of Variance and Fisher's Protected Least Significant Difference.

## 3. Results

### 3.1. Locomotor activity

When tested 4 h after the implantation of osmotic minipumps containing methylphenidate, there was a large, significant increase in locomotor activity, compared to animals receiving continuous infusions of saline (Fig. 1A). Over the 7 day treatment period, behavior remained elevated and fairly stable, with no tolerance or sensitization observed. Similar results were seen for stereotypy. Methylphenidate produced a significant amount of stereotypy,

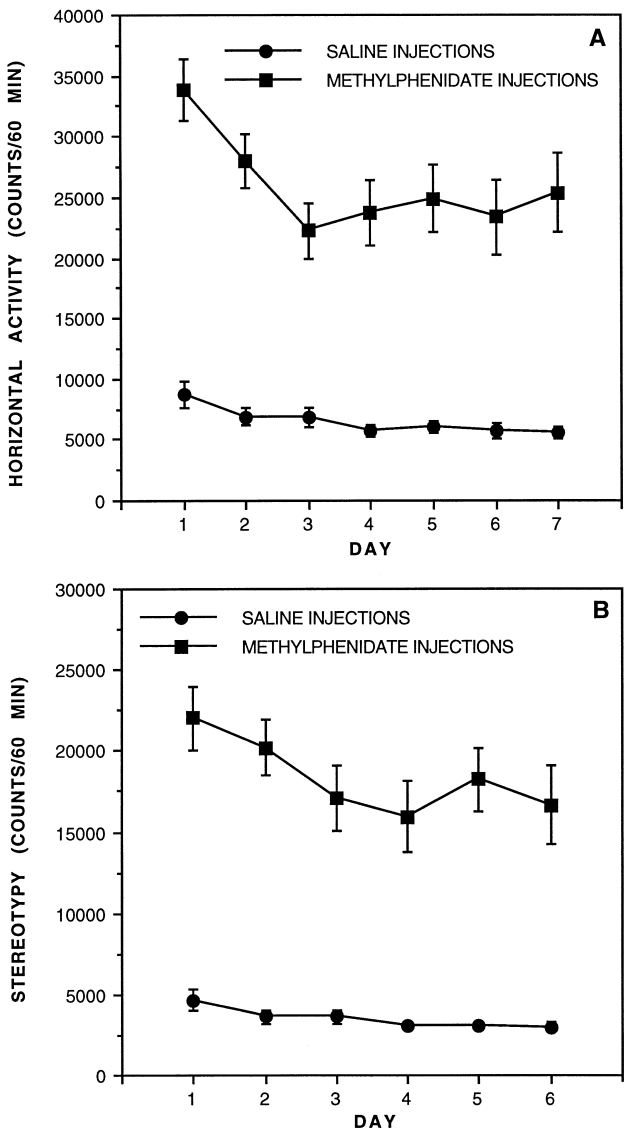


Fig. 2. Horizontal locomotor activity (A) and stereotypy counts (B) in animals treated with methylphenidate ($n = 12$) or saline ($n = 12$) via daily i.p. injections. Activity tests were conducted for 1 h each day, and the data are represented as counts per 60 min observation period. Both horizontal activity and stereotypy were significantly elevated in the methylphenidate group, vs. control, on each day of testing ($P < 0.05$). Both measures in the methylphenidate group decreased significantly over the course of the treatment period, as compared to day 1. Data are means ± S.E.M.

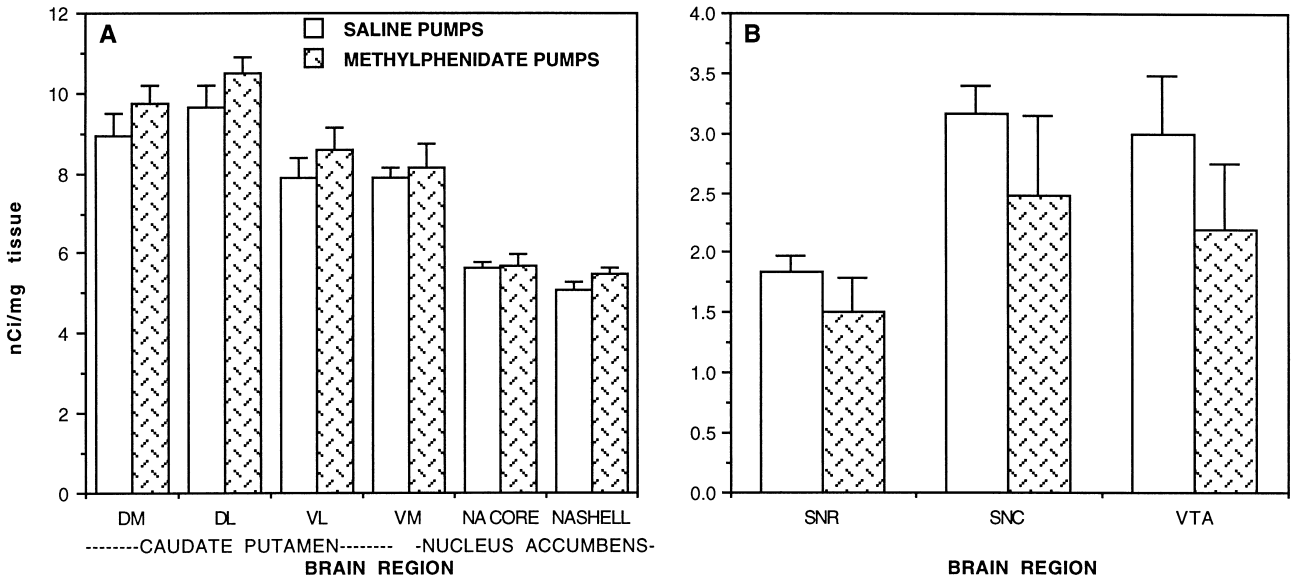


Fig. 3. Densitometric analysis of [$^{125}$I]RTI-121 binding in caudate of rats treated for 7 days with a continuous infusion of methylphenidate or saline. (A) Binding in the caudate putamen and nucleus accumbens. (B) Binding in the substantia nigra and ventral tegmental area. Abbreviations: DM, dorsomedial; DL, dorsolateral; VL, ventrolateral; VM, ventromedial; SNC, substantia nigra compacta; SNR, substantia nigra reticulata; VTA, ventral tegmental area. There were no significant alterations in transporter density in any of these brain regions.

and the level remained constant throughout the week (Fig. 1B).

Methylphenidate produced a large, significant increase in locomotor activity immediately after the first injection (Fig. 2A). Following repeated daily injections of methylphenidate, a partial tolerance to the locomotor activating effects occurred (Fig. 2A). The amount of activity on day 1 was significantly greater than that seen on days 3–7 ($P < 0.01$). By day 3 of the study, behavioral activity reached a plateau significantly lower than that which was seen on day 1, but still significantly greater than observed in saline treated animals. Similar results were seen for stereotypy. Methylphenidate produced a significant amount of stereotypy on day 1 and while still significantly greater than saline, was significantly decreased on days 3–7 (Fig. 2B).

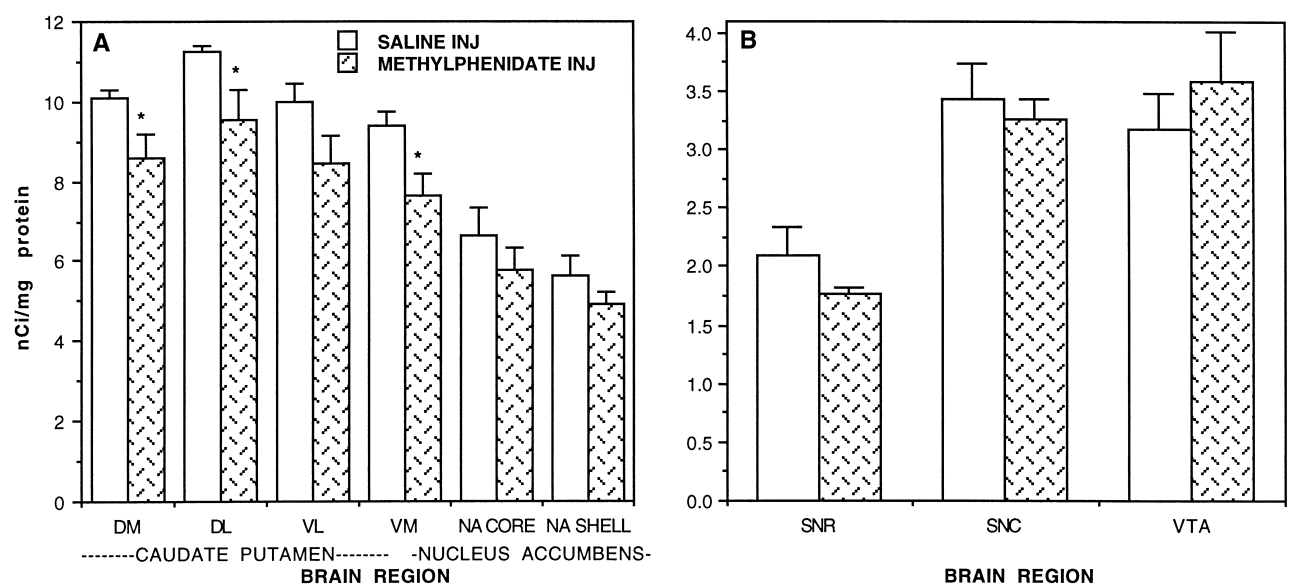


Fig. 4. Densitometric analysis of [$^{125}$I]RTI-121 binding in caudate of rats treated for 7 days with daily injections of methylphenidate or saline. (A) Binding in the caudate putamen and nucleus accumbens. (B) Binding in the substantia nigra and ventral tegmental area. Abbreviations: DM, dorsomedial; DL, dorsolateral; VL, ventrolateral; VM, ventromedial; SNC, substantia nigra compacta; SNR, substantia nigra reticulata; VTA, ventral tegmental area. * $P < 0.05$ compared to saline.

### 3.2. Dopamine transporter binding

Continuous infusion with methylphenidate did not produce any alterations in dopamine transporter density in either the caudate putamen, nucleus accumbens, substantia nigra, or ventral tegmental area (Fig. 3). In contrast, at the end of 7 days of daily injections, the density of dopamine transporters in the caudate putamen was significantly decreased in the animals receiving methylphenidate, as compared to saline ($P < 0.05$; Fig. 4A). Binding was decreased by approximately 20% in most regions of the caudate putamen. In contrast, while there were trends towards decreases, there were no significant alterations in binding in either the core or shell of the nucleus accumbens (Fig. 4A) or in the substantia nigra or ventral tegmental area (Fig. 4B). There were no significant changes in transporter density in more caudal sections of the caudate putamen after either treatment (data not shown).

## 4. Discussion

Chronic treatment with methylphenidate for 7 days produced significant alterations in both behavior and the density of dopamine transporters. These changes were dependent upon the paradigm by which the drug was administered. Although methylphenidate produced significant increases in locomotor activity over the entire treatment period, the adaptations observed over the course of the treatment period were considerably different from those generated by cocaine.

Using the present dosing paradigm, we have previously shown that a continuous infusion of cocaine produces an initial increase in activity, to which a partial tolerance is observed (Kunko et al., 1998). This pattern of behavior is only partially mimicked by selective dopamine uptake inhibitors, and is not produced by selective norepinephrine or serotonin uptake inhibitors (Izenwasser et al., 1999). Methylphenidate, on the other hand, produced a significant increase in locomotor activity that remained constant throughout the 7 day treatment period. This was different than the pattern produced by either cocaine (Kunko et al., 1998), or the selective dopamine uptake inhibitors RTI-117 (a compound structurally similar to cocaine) or GBR 12909 (Izenwasser et al., 1999). A major difference between cocaine and methylphenidate is that methylphenidate has a very low affinity for the serotonin transporter (Pan et al., 1994). The ratio of affinity for the serotonin vs. the dopamine transporter for cocaine is approximately 10 (Carroll et al., 1995), whereas for methylphenidate it is 92 (Pan et al., 1994). Both compounds have a lower affinity for the norepinephrine than the dopamine transporter (Pan et al., 1994; Carroll et al., 1995). Since methylphenidate produced such a different pattern of behavior than cocaine during the treatment period, it is possible that inhibition of serotonin uptake has some effect on the behavioral adaptations that occur during a continuous infusion of cocaine.

The initial injection of methylphenidate produced a significant increase in locomotor activity. Subsequent injections, however, produced significantly less activity than on day 1, with a plateau reached by day 3 of the treatment period. Full tolerance was not achieved over the 7 days of treatment. These data are in agreement with the finding that a lower dose of methylphenidate (20 mg $kg^{-1}$ $day^{-1}$) produces an increase in locomotor activity, and that this decreases over time (McNamara et al., 1993). In fact, the doses tested on locomotor activity were approximately equal since the dose in the current study was administered in two daily injections. The dose that was administered immediately prior to behavioral testing was 18 mg $kg^{-1}$, with the remainder of the daily 44 mg $kg^{-1}$ dose administered 4 h later. In contrast to the previous study (McNamara et al., 1993) where activity levels continued to decrease up to day 7, a plateau is reached by day 3 of treatment, and this level of activity is maintained throughout the 7 day period. Since it is generally understood that tolerance develops more quickly the higher a dose of drug, this is likely due to the higher daily dose employed in the present study, and it is likely that a plateau would be reached at a later time with a lower dose. Our data and the findings of McNamara et al. (1993) are in contrast to a recent report of sensitization to methylphenidate (Gaytan et al., 1997a). However, a number of major differences between that study and the current study provide possible explanations for the report of sensitization. Rats were injected with a range of doses on 1 day, then injected with 2.5 mg $kg^{-1}$ $day^{-1}$ for 5 more days and then challenged after 6 days of no drug. Sensitization on horizontal activity was observed only at a dose of 0.6 mg $kg^{-1}$, and was not seen at doses of 2.5 and 10 mg $kg^{-1}$ (Gaytan et al., 1997a). Thus, the doses used were much lower than in the present study. In addition, the challenge dose was administered after 6 days of no drug administration. It is likely that the observed sensitization is a compensatory response to the prior tolerance that might have been observed during the course of the drug administration.

It is not known why chronic administration of methylphenidate would lead to behavioral adaptations in the opposite direction of cocaine. Acutely, both drugs stimulate locomotor activity, yet with repeated injections of cocaine, sensitization is produced (Reith et al., 1987; Kalivas et al., 1988; Segal and Kuczenski, 1992). Methylphenidate, unlike cocaine, does not appear to have a high abuse potential, in that it is not widely abused regardless of its widespread availability. Since methylphenidate, as mentioned above, lacks affinity for the serotonin transporter while inhibiting dopamine uptake more potently than norepinephrine uptake, it is possible that the inhibition of serotonin uptake in some way contributes to the sensitization observed with repeated cocaine injections, and poten-

tially to the abuse potential associated with the drug. We do know that a serotonin uptake inhibitor alone does not produce increases in locomotor activity with this same treatment paradigm (Izenwasser et al., 1999), however, a modulatory role cannot be ruled out. This suggestion is consistent with the recent report that cocaine is self-administered in dopamine transporter knockout mice, implying that other systems, such as the serotonin system may be important in the actions of cocaine (Rocha et al., 1998).

Another possibility is that the kinetic differences between cocaine and methylphenidate contribute to the observed behavioral changes during a period of repeated treatment. In humans, methylphenidate rapidly enters the brain (time to peak concentration is 4–10 min) as does cocaine (time to peak concentration is 2–4 min) (Volkow et al., 1995). The half-peak clearance is approximately 20 min for cocaine and 90 min for methylphenidate (Volkow et al., 1995). It is unlikely that the changes in behavior are due merely to the slightly longer half-life of the methylphenidate, as compared to cocaine. If this were the case, one would anticipate that the continuous infusion of methylphenidate or cocaine, where the drug level remains constant over the entire treatment period, (Kunko et al., 1998) would have produced even bigger changes than did daily injections.

It is clear from the stereotypy data, that stereotypic behavior was not responsible for the patterns of horizontal activity that were seen. Previously it was reported that methylphenidate produces stereotypy and that this might interfere with the ability of the animal to exhibit forward locomotion (Mueller, 1993; Gaytan et al., 1996; Gaytan et al., 1997b). In the present study, levels of stereotypy followed the same pattern over time as did horizontal activity. Animals receiving daily injections of methylphenidate showed an initial increase in activity on day 1, with a significant diminishment over time. This was true for both horizontal activity and stereotypy. Thus, there did not appear to be an increase in stereotypy to account for the decrease in forward locomotion and partial tolerance developed to both measures. Similarly, in the animals continuously infused with methylphenidate, stereotypy remained constant over the entire course of treatment, as did horizontal activity.

When dopamine transporter density was measured in the brains of the animals who had been injected with methylphenidate, a small but significant decrease in density was observed in the caudate putamen. No significant change was seen in the nucleus accumbens. This suggests that the decrease seen in the caudate was not merely due to residual methylphenidate, since it should have equally remained in both brain regions. It is not clear whether this decrease in transporter density in the caudate putamen is responsible for the partial tolerance to the locomotor activating effects of the drug during the injection period, but the two findings are consistent. This finding is again in contrast to cocaine, which produces no changes in the density or affinity of dopamine transporters (Izenwasser and Cox, 1990; Kunko et al., 1997).

These studies show that a sensitized response to methylphenidate does not occur with repeated administration, unlike cocaine. In contrast, a partial tolerance to the behavioral activating effects of the drug occurs. These findings suggest that serotonin may play an important role in the adaptive responses to chronic cocaine, whether cocaine is administered via intermittent injections or via continuous infusion.

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