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Pharmacology, Biochemistry and Behavior 81 (2005) 198 – 204

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Relation between methamphetamine-induced monoamine depletions in the striatum and sequential motor learning

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Received 1 December 2004; received in revised form 18 March 2005; accepted 23 March 2005
Available online 29 April 2005

Abstract

Methamphetamine (METH) use results in depletion of monoamines in the striatum. The purpose of this study was to evaluate the relation between the degree of METH-induced monoamine depletion in the striatum and impairment on a striatally-dependent learning task in rats. Male Sprague–Dawley rats received four injections of METH (10 mg/kg) or saline at 2-h intervals. METH treatment produced a 38.5% (±5.6) and 46.7% (±6.7) dopamine (DA) depletion in the medial and lateral striatum, respectively. Serotonin (5-HT) was depleted 15.6% (±10.4) and 21.1% (±8.2) in the medial and lateral striatum, respectively. One month after treatment, rats were trained on a sequential-memory task on an 8-arm radial maze. METH-treated rats made significantly fewer direct movements between arms in the maze sequence across days of trials. The learning impairment was significantly correlated with the degree of DA depletion in the medial striatum, as well as serotonin tissue content in striatum. Only rats with a greater than 40% DA depletion in medial striatum showed significant impairments. These results provide additional evidence for METH-induced learning impairments and suggest that this impairment is dependent on the striatal monoamine loss, in general, and the degree of DA loss in medial striatum, in particular.

Keywords: Procedural learning; Dopamine; Serotonin; Basal ganglia; Neurotoxicity; Sequential learning

1. Introduction

Exposure to METH causes significant alterations in central monoamine systems in humans (Volkow et al., 2001a; Wang et al., 2004; Wilson et al., 1996) and nonhuman primates (Woolverton et al., 1989). Likewise, rats exposed to high doses of METH have significant monoamine depletions in the striatum (Hotchkiss and Gibb, 1980; Ricaurte et al., 1982, 1980; Wagner et al., 1980). While these monoamine losses are less than those observed, for example, in Parkinson's disease patients (McCann et al., 1998), it is likely that they affect the functioning of the striatum (Chapman et al., 2001; Johnson-Davis et al., 2002; Nisenbaum et al., 1996). Given that the striatum is integrally involved in motor control and procedural learning (McDonald and White, 1993; Packard et al., 1989; White and McDonald, 2002), long-lasting changes in striatal monoamine systems are likely to affect organismal behavior.

While METH-treated animals do not display gross motor deficits such as those seen in human patients with Parkinson's disease, several studies have noted learning deficits on particular tasks. In rodent studies, rats treated with neurotoxic regimens of METH show deficits in active avoidance and balance beam performance (Walsh and Wagner, 1992), impaired performance on the Morris water maze task (Friedman et al., 1998), impaired performance on object recognition tasks (Schroder et al., 2003), and decreased locomotor responses to METH challenge (Wallace et al., 2001). Previous work from our laboratory has shown that prior treatment with a neurotoxic regimen of

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doi:10.1016/j.pbb.2005.03.010

METH impairs sequential motor learning on a radial-arm maze (Chapman et al., 2001) and alters gene expression long-term in striatonigral, but not striatopallidal, neurons (Chapman et al., 2001; Johnson-Davis et al., 2002). METH use in humans has also been shown to be associated with motor slowing and memory impairments (Rogers et al., 1999; Volkow et al., 2001b). While such studies suggest that METH has consequences for striatal-dependent behaviors, still little is known about the relationship between the partial monoamine loss produced and the deficits in striatal-dependent learning. The purpose of the present study therefore was to further examine the relation between the degree of monoamine loss induced by METH in different subregions of the striatum and the observed deficits in sequential motor learning.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (~300 g; Simonsen Laboratories, Gilroy, CA) were housed in hanging wire cages in a room controlled for temperature and lighting (12:12 h) and allowed free access to food and water. Prior to behavioral testing, rats were food restricted to 85–90% of free-feeding weight. All animal care and experimental manipulations were approved by the Institutional Animal Care and Use Committee of the University of Utah, and were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Methamphetamine treatment

(±)-Methamphetamine hydrochloride was provided by the National Institute on Drug Abuse (Rockville, MD). Drug doses were calculated as the free base. The night before the drug treatment, the rats were weighed and rehoused in plastic tub cages (33-cm length × 28-cm width × 17-cm height; 8 rats per tub). The next day, rats received four injections of either saline (control) or METH (10 mg/kg, s.c.), at 2-h intervals. Body temperatures were monitored via a rectal probe every 30 min during the injection procedure. If a rat's core temperature exceeded 41 °C, the rat was removed from the group tub cage and put alone in another tub cage over ice to decrease the hyperthermia. Two hours after the last injection, the rats were returned to their home cages and given free access to food and water.

2.3. Sequential motor learning task

Ten days after treatment with METH, the rats were transported to new housing and food intake was restricted as described above. The rats were handled daily for 3 days and then exposed to the radial-arm maze and the testing room. The radial-arm maze consisted of an octagonal (30-cm wide) center platform with eight arms (50 cm in length) leading from the center platform to a food well (2-cm wide and 1-cm deep) at the distal end of each arm in which food rewards (whole Froot Loops, Kellogg Company, Battle Creek, MI) were placed. There was a Plexiglas door at the entry into each arm from the center platform. Rats were allowed free access to all of the arms for 15–20 min per day for 5 consecutive days to habituate them to the testing environment and food reward.

Three weeks after METH administration, the behavioral training began. During pretraining to fully habituate the rats to the task, the rats were given a fixed sequence of six maze-arm openings. That is, the rat was placed in the center of the maze with all doors leading out from center platform closed. The first door in the sequence was opened and the rat was allowed to move to the food well to collect its reward. Upon entrance of the rat into the first arm, the door to the next arm in the sequence was opened. As the rat moved to the next door/arm in the sequence, the door to the arm just visited was closed, and then the next door in the sequence was opened while the rat was in the preceding arm. The rats completed four trials of the sequence of six door openings a day for 5 successive days, using the same sequence of door openings for each trial every day. This pretraining phase was included to avoid contamination of the behavioral results by effects of METH toxicity on the rat's ability to generally learn how to perform this task. Previous work in our lab had indicated that early performance on this task involves not only learning the sequential information, but also simply how to perform on the task (Chapman et al., 2001).

Once the 5 days of pretraining were complete, the rats were then tested on a new fixed sequence of door openings to assess the impact of METH-induced neurotoxicity on sequential learning per se. Each rat was given a new fixed sequence of six maze-arm door openings for 5 days. All rats in this study were given the same sequence of door openings to avoid confounds due to differences in the difficulty of the sequences of door openings.

2.4. Dependent measures

Five dependent measures were used to assess the rat's performance on the sequential learning task: total run time, center-platform time, arm time, direct movements, and the increase in direct movements (difference in direct movements between the first and last day of training). The total run time was defined as the total time taken for the rat to retrieve the food rewards from arms 2 to 6 (the first arm in the sequence was excluded to avoid variation in the time to retrieve the first reward arising from how the rat was placed in the center platform to initiate the trial). The total run time was calculated by summing the time taken by the rat to retrieve each food reward after exiting the previous door in the sequence for arms 2

through 6. The time taken by the rats to eat the food reward and exit the arm was not included. The five times were then summed to give the total run time for the trial. The center-platform time was defined as the amount of time spent in the center platform (excluding the time prior to entry into the first door). The arm time was calculated as the sum of the time the rat spent running down the second through sixth maze arms until the food reward was reached in each arm. "Direct movements", which are similar to the "bearing" measure previously described by Vorhees and colleagues (Vorhees et al., 2000), were defined as progression from the previous arm through the center platform to the next door in the sequence without the rat stopping or touching any wall or closed door of the center platform. Total time measurements in the study were recorded on-line during behavioral testing. Center times, arm times and direct movements were coded from video tape recordings of all trials. For all time measures, the values obtained for the four daily trials were then averaged to give one value per animal per day. For the direct movement measure, the number of direct movements was summed across the four daily trials.

2.5. Monoamine tissue content

Thirty minutes after the last behavioral trial (9 weeks after METH treatment) the rats were sacrificed by exposure to CO_2 for 1 min. Rats were then decapitated, and the brains were removed rapidly and frozen in 2-methyl-butane (10 s) chilled on dry ice. Brains were stored at −20 °C until processed for monoamine tissue content. The dopamine (DA) and serotonin (5-HT) content in striatal tissue were determined by taking a tissue section from the medial and lateral aspect of the dorsal striatum of one hemisphere from each brain. This was accomplished by taking a 1-mm thick section of the striatum (~1.2 mm anterior to bregma), laying the section flat on a chilled surface, and dissecting the medial and lateral striatal regions. Brain samples were then put into tissue buffer [200 μl; 0.05 M sodium phosphate/0.03 M citric acid buffer with 25% methanol (v/v), pH 2.5], sonicated, and centrifuged. Ten microliters of supernatant was injected onto a high pressure liquid chromatography system coupled to an electrochemical detector (Eox=+0.6 V; Decade detector, Antech-Leyden, The Netherlands) for separation and quantification of DA and 5-HT levels as previously described (Chapin et al., 1986). A Whatman PartiSphere C-18 column (250×4.6 mm, 5 μm) was used to separate the monoamines. The mobile phase consisted of MeOH (23% v/v), sodium octyl sulfate (0.03% w/v), EDTA (0.1 mM), sodium phosphate dibasic (0.05 M) and citric acid (0.03 M). The pH of the mobile phase was 2.87, and the flow rate was 0.5 ml/min. To adjust for variability in the size of the tissue samples, all values were expressed per milligram protein. Protein content was determined with the Lowry protein assay.

2.6. Data analysis

The performance of saline- and METH-pretreated rats on the sequential motor learning task was compared across days of trials using a 2-factor ANOVA with repeated measures across days of training. Post hoc analysis was accomplished using unpaired *t* tests at individual time points to determine significant differences. Differences in the degree of learning as reflected by the change in number of direct movements over days 1–5 were analyzed using a one-way ANOVA followed by post hoc comparisons using a Dunnett's two-tailed test. Correlation coefficients were determined by a simple regression analysis using *Super*-ANOVA software (Abacus Concepts, Inc., Berkeley, CA). In all cases, statistical significance was set at $p \leq 0.05$.

3. Results

3.1. Monoamine depletions

METH administration decreased DA tissue content by 38.5% (±5.6, mean±SEM; Table 1) in the medial striatum and 46.7% (±6.7) in the lateral striatum. The range of DA depletions was 16.9–76.7% in the medial striatum and 3.9–80.2% in the lateral striatum. 5-HT content was decreased by 15.6% (±10.4) in the medial striatum and 21.1% (±8.2) in the lateral striatum. The range of 5-HT depletions was 0.0–77.5% in the medial striatum and 0.0–75.7% in the lateral striatum.

3.2. Effects of prior METH administration on sequential motor learning

METH-treated rats showed a trend towards slower total run times to complete the task [$F(1,15)=2.49$, $p=0.14$; Fig. 1A], as well as a trend towards greater center-platform times [$F(1,15)=2.51$, $p=0.13$; Fig. 1B]. There was no significant difference between the METH-treated and saline-treated rats in the arm times [$F(1,15)=0.12$, $p=0.73$; Fig. 1C]. However, METH-treated rats showed significantly less learning as evidenced by the number of direct movements made in later trials. That is, the ANOVA showed a significant interaction when comparing the direct movements of the METH-treated rats vs. the saline-treated controls [$F(4,60)=4.85$, $p=0.002$; Fig. 1D]. Post hoc

Table 1
Monoamine content in striatum of control (saline) and METH-treated rats

	Dopamine		Serotonin	
	Medial	Lateral	Medial	Lateral
Saline	173.0±14.2	189.7±19.6	9.9±0.8	8.5±1.1
METH	106.3±9.7	101.2±12.6	8.3±1.0	6.7±0.7

DA and 5-HT tissue content measured 9 weeks after administration of saline or METH. Values are expressed as ng/mg protein±SEM ($n=6$ for saline and $n=11$ for METH).

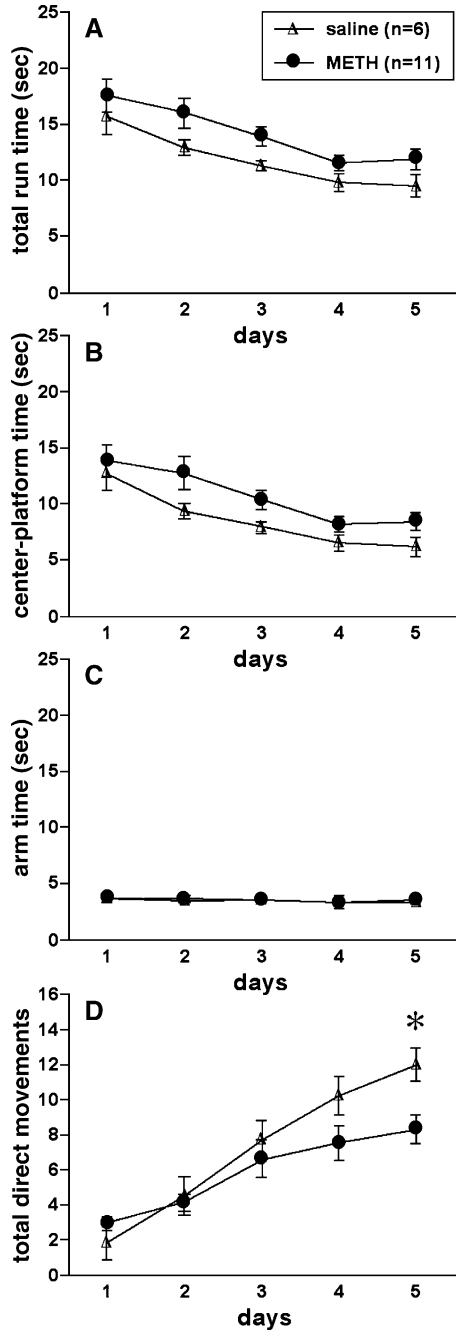

Fig. 1. Effects of prior exposure (>3 weeks prior to testing) to a neurotoxic regimen of METH (10 mg/kg, s.c. 4 times at 2-h intervals) on total run time (A), center-platform time (B), arm time (C), and direct movements (D). Values are mean times over four daily trials (±SEM) for (A–C) and total number of direct movements over four daily trials (±SEM) for (D). *Significantly different from saline-treated controls, $p \leq 0.05$.

analysis revealed that the METH-treated rats made significantly fewer direct movements on the last day of training ($t = -2.57$, $p = 0.02$; Fig. 1D).

The degree of DA depletion in the medial striatum was negatively correlated with the increase in the number of direct movements across days 1–5 ($r^2 = 0.35$, $p = 0.05$; Fig. 2A). There was no significant correlation between the degree of DA depletion in the lateral striatum and this measure of learning ($r^2 = 0.17$, $p = 0.21$; Fig. 2B). There also was a significant correlation between 5-HT tissue *content* in the lateral striatum and the increase in the number of direct movements made ($r^2 = 0.42$, $p = 0.03$; Fig. 2D), and a trend between 5-HT *content* in the medial striatum and this measure ($r^2 = 0.34$, $p = 0.06$; Fig 2C). However, the effects of METH on 5-HT levels in the striatum were quite variable, with some rats not showing 5-HT depletions in response to METH relative to controls. When only the METH-treated rats with 5-HT depletions were included in the analysis,

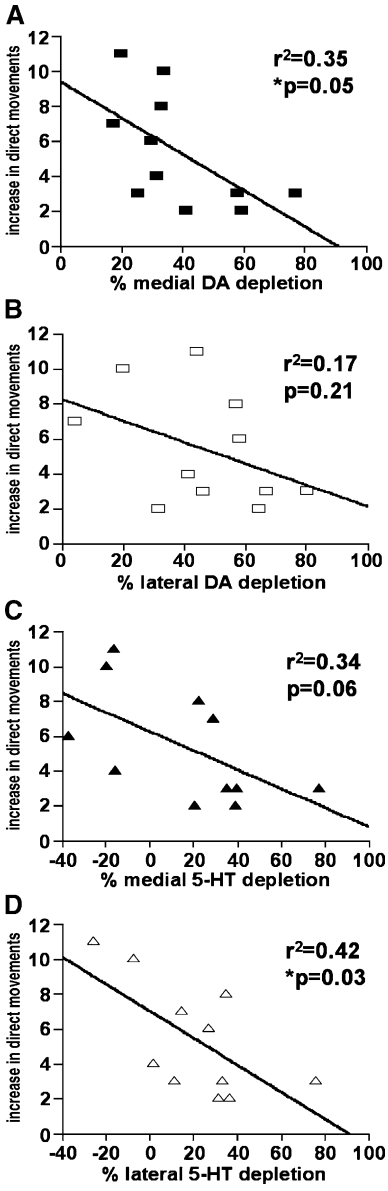

Fig. 2. Correlations between the increase in direct movements from the first to the last day of training and the degree of monoamine depletion in the medial and lateral striatum. Increases in direct movements were obtained by subtracting the number of direct movements made by each rat on the first day of the fixed-sequence of door openings from the total number made on the last day of the fixed-sequence of door openings. Dopamine (DA) and serotonin (5-HT) depletions were determined by HPLC and electrochemical detection for separation and quantification. *Significantly correlated, $p \leq 0.05$.

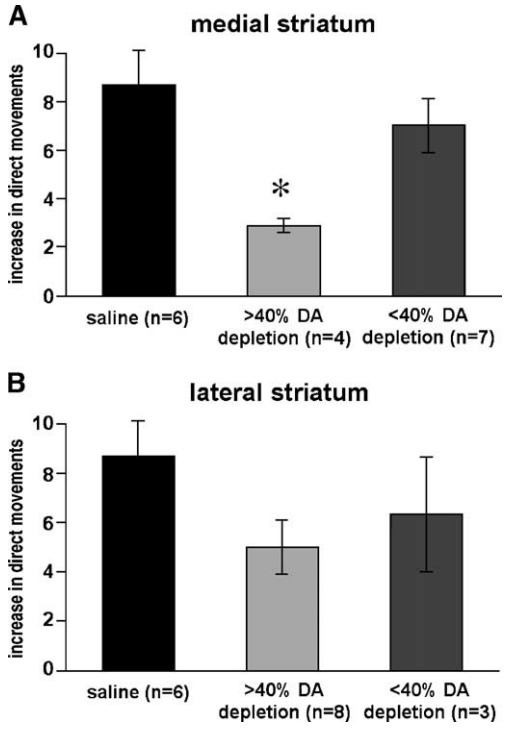

Fig. 3. Increase in direct movements from the first to the last day of training for rats with >40% DA depletion and rats with <40% DA depletion (±SEM) in the medial (A) and lateral striatum (B). Values were obtained by subtracting the number of direct movements made by each rat on the first day of trials from the total number made on the last day of trials. *Significantly different from saline-treated controls, $p \leq 0.05$.

there was no correlation between the degree of 5-HT *depletion* in the lateral ($r^2=0.04$, $p=0.60$, $n=9$) or medial ($r^2=0.11$, $p=0.46$, $n=7$) striatum and the increase in direct movements (data not shown).

Given the significant correlation between the degree of DA depletion in the medial striatum and the performance on the learning trial, we further examined the relation between the degree of DA loss and the learning. A one-way ANOVA revealed a significant difference between groups [$F(2,14)=5.75$, $p=0.02$], with only rats with a greater than 40% DA depletion in the medial striatum showing less increase in direct movements between days 1 and 5 relative to controls on post hoc analysis (Fig. 3). There was no such relationship between the degree of 5-HT loss and learning (data not shown). However, it should be noted that those rats with a greater than 40% loss of dopamine in the medial striatum also had significantly greater loss of 5-HT in the medial striatum than did the rats with less marked DA depletion ($t=-2.44$, $p=0.04$).

4. Discussion

These experiments provide further evidence that a neurotoxic regimen of METH causes monoamine depletions in the striatum and impairs the learning of implicit sequential motor information (procedural memory) in a radial-arm maze task. Furthermore, the present data extend those of previous studies by demonstrating that this behavioral impairment is significantly correlated with the striatal monoamine loss in general and with the degree of DA loss in medial striatum, in particular. The findings suggest that at least a 40% loss of DA in the medial striatum is necessary in order to observe impairments on such an implicit learning task.

Monoamines are thought to be critically important in proper learning and memory function of the mammalian brain. Both DA and 5-HT are implicated in learning and memory, although the literature suggests that they have differing roles in the process of memory formation. DA depletions have been shown to impair learning and memory function in rats (Amalric and Koob, 1987; Baunez and Robbins, 1999; Mason and Iverson, 1974; Robbins et al., 1990), and the DA innervation of the striatum appears to be critical for the implicit learning of motor sequences (Matsumoto et al., 1999). Furthermore, DA has been implicated as a major player involved in the plastic changes thought to occur within the striatum during normal procedural learning and implicit memory function (Arbuthnott et al., 2000; Centonze et al., 2001; Reynolds and Wickens, 2000; Tang et al., 2001). Based on these data, it could be inferred that the decreased levels of DA in the medial striatum induced by METH impair the ability of neurons within striatum to undergo the proper plastic changes required to produce normal sequential motor learning.

Whereas evidence implicates striatal dopamine in normal procedural learning function in general and sequential motor learning in particular, the role of 5-HT systems, especially the 5-HT innervation of the striatum, in such processes is largely unknown. At present, we cannot rule out a contribution of the striatal 5-HT depletion to the behavioral deficits observed in this study. Clearly further work is needed to determine the contribution of striatal 5-HT depletions, such as those obtained in the present study, to deficits in procedural learning.

The 5-HT innervation of the prefrontal cortex has been shown to play a critical role in reversal learning/behavioral inhibition (Clarke et al., 2005), and neurotoxic regimens of METH can produce cortical 5-HT depletions (Abekawa et al., 1997; Armstrong and Noguchi, 2004; Green et al., 1992; Ohmori et al., 1993). The rats in the present study learned one fixed sequence of maze-door openings to fully habituate them to the task, and then were given the second fixed sequence of door openings to test their learning of sequential information (independent of learning general task demands). It is therefore possible that the deficits observed in the learning of this second sequence reflect impaired ability of the rats to inhibit the first sequence as a consequence of cortical 5-HT loss. However, analysis of the errors made by the rats during the learning of the second fixed sequence failed to reveal any difference in the number of perseverative errors made by the METH-treated rats

relative to controls (data not shown). Furthermore, previous work from our lab has shown impairments on the acquisition of just one fixed sequence (Chapman et al., 2001). Therefore, we think that a loss of behavioral inhibition due to cortical 5-HT depletion does not likely underlie the behavioral deficits observed in the present study.

The idea that the striatum is important for proper procedural learning is supported by human research. Brain imaging using fMRI has shown that dynamic neural changes, thought to be related to plasticity, occur in the striatum in the process of skilled motor learning (Ungerleider et al., 2002). As in the human work, studies of rodents support a role for the striatum in procedural learning. Lesions of the rodent striatum produce learning impairments in the win-shift task on the radial arm maze (Packard et al., 1989), visual discrimination task in the Morris water maze (Packard and McGaugh, 1992), and response learning in the plus maze (Packard and McGaugh, 1996). Overall, these studies clearly implicate the striatum in motor-response learning. Although this study and previous work (Chapman et al., 2001; Friedman et al., 1998; Vorhees et al., 2000; Wallace et al., 2001; Walsh and Wagner, 1992) suggest that METH treatment produces deficits in learning and memory function, the specific subregions of the brain affected by METH that contribute to such deficits are still largely unknown.

Previously published studies that have examined the behavioral role of specific subregions of the striatum have suggested a contrasting role of the medial and lateral striatum in response learning. Specifically, studies in which excitotoxic lesions were restricted to the medial striatum have implicated this subregion in more complicated forms of learning, such as reversal learning on a T-maze task (Ragozzino et al., 2002) and the learning of multiple motor sequences (DeCoteau and Kesner, 2000). In particular, Kesner and colleagues found that excitotoxic lesions of the medial, but not the lateral, striatum caused a complete inability to learn a motor sequence in a radial-arm maze task analogous to that used in the present study (DeCoteau and Kesner, 2000). Importantly, hippocampal lesions did not impair performance on this task, highlighting the critical role of intact basal ganglia function for normal sequential motor learning on this radial arm maze task. Our results showing that learning on this task was negatively correlated with the degree of DA depletion in the medial, but not the lateral striatum, provides further evidence for an important role of the medial striatum in implicit learning of motor sequences. These data also further suggest that DA modulation of this region of striatum may play a critical role in the neural plasticity associated with procedural learning and implicit memory.

Our results further suggest that at least a 40% DA depletion in the medial striatum is required to produce a behavioral deficit in procedural learning on this radial-arm maze task. Our data therefore suggest that a greater than 40% loss of DA in the medial striatum, as a consequence of METH abuse or disease, may lead to impaired basal ganglia function. The loss of dopamine input to the striatum as a result of Parkinson's disease is associated with deficits in procedural learning in human patients (Ferraro et al., 1993; Heindel et al., 1989; Knowlton et al., 1996; Roncacci et al., 1996; Saint-Cyr et al., 1988), and dopaminomimetic therapy has been shown to improve cognition in some patients with Parkinson's disease (Mohr et al., 1989). While the gross motor symptoms of Parkinson's disease appear only after substantial degeneration of the dopaminergic system (i.e. a 70–80% decrease in striatal DA (Bernheimer et al., 1973)), our data show that a much smaller DA depletion (40%) in the medial striatum is associated with deficits in sequential motor learning in rodents. Although the contribution of striatal 5-HT loss to such deficits is currently unknown, these findings suggest that sequential motor learning tasks may be useful in the early diagnosis of diseases such as Parkinson's disease. Interestingly, human METH users have shown partial reductions in dopamine transporter levels in the caudate and putamen (McCann et al., 1998; Volkow et al., 2001a), and these reductions have been shown to be correlated with impairments in motor function and memory tasks (Volkow et al., 2001b). Understanding the degree of monoamine depletion that is required to produce other types of memory impairment and the brain regions most affected by such loss of monoamines would help in the further understanding of how to diagnose and treat human disorders that affect the basal ganglia, such as Parkinson's disease and stimulant abuse.

Acknowledgement

This research was funded by DA13367.

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