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In Vivo Dialysis Measurements of Dopamine and DOPAC in Rats Trained to Turn on a Circular Treadmill

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SABOL, K. E., J. B. RICHARDS AND C. R. FREED. *In vivo dialysis measurements of dopamine and DOPAC in rats trained to turn on a circular treadmill.* PHARMACOL BIOCHEM BEHAV **36**(1) 21–28, 1990.—In vivo dialysis was used to measure extracellular fluid concentrations of dopamine and dihydroxyphenylacetic acid (DOPAC) in rats which were trained to run on a circular disk treadmill for water reinforcement. Turning resulted in bilateral increases in DOPAC in lateral striatum as well as nucleus accumbens/medial striatum. Dopamine release showed small but not significant increases at both sites. Changes in DOPAC release were not lateralized. Free drinking without circling also resulted in significant increases in DOPAC in these two brain areas. During free drinking, dopamine release was significantly increased in lateral striatum but not in nucleus accumbens/medial striatum. These experiments indicate that dopamine metabolism is increased in rat striatum and nucleus accumbens in animals running on circular treadmills as well as by free drinking.

In vivo dialysis Dopamine DOPAC Circling Conditioned behavior Striatum Nucleus accumbens

UNILATERAL lesions of the dopamine system cause rats to have a turning bias in which they spontaneously rotate in the direction ipsilateral to the side of the lesion. This ipsilateral rotation is enhanced by administration of the catecholamine releasing agent amphetamine (20). Based on this relationship between lateralized dopamine release and postural asymmetries, previous studies in our laboratory tested the hypothesis that nonlesioned rats which were trained to rotate in one direction would demonstrate a corresponding dopaminergic asymmetry. Rats which were trained to circle for a sucrose/water reward were implanted with in vivo electrochemical electrodes. Recordings showed an apparent increase in striatal dopamine release on the side of the brain contralateral to the direction of turning (21). In both the lesioned and the trained turning models, the direction of rotation was opposite to the side of the brain with the higher dopamine release.

There is a well-documented distinction between mesolimbic and nigrostriatal dopamine function. For example, dopamine in nucleus accumbens appears to mediate locomotor responses (8,13) while striatal dopamine is associated with stereotypy (8). Freed and Yamamoto (6) studied rats forced to run in place on a rotating disk treadmill and found that increases in nucleus accumbens dopamine and DOPAC concentrations were closely related to speed and direction of movement, while changes in striatal dopamine and DOPAC were more associated with body arc or posture. In both nucleus accumbens and striatum, the increases in dopamine and DOPAC were greater on the side contralateral to the circling direction.

As a followup to these prior studies, we have now applied the technique of in vivo dialysis to study dopamine and DOPAC release directly from nucleus accumbens and striatum of moving animals. The trained movement task in the present experiments was different from that used in the past. Because the dialysis technique requires inflow and outflow tubing to be attached to the rat's head, animals were trained to run in place on a rotating disk treadmill rather than turning 360 degrees in space. With this device, the animal maintained an arched posture as he propelled the disk. Freed and Yamamoto using the tissue assay technique and a forced treadmill paradigm demonstrated that body arc appeared to be an important characteristic for causing contralateral increases in accumbens and striatal dopamine and DOPAC (6). By retaining this variable in the inplace turning paradigm, we looked for evidence of lateralized release and metabolism of dopamine and DOPAC as suggested by the findings of Yamamoto *et al.* (21), Yamamoto and Freed (22,23), Morgan *et al.* (11), Freed and Yamamoto (6) and Bennett and Freed (2).

METHOD

Animals

Twenty male Sprague-Dawley rats weighing between 300 and

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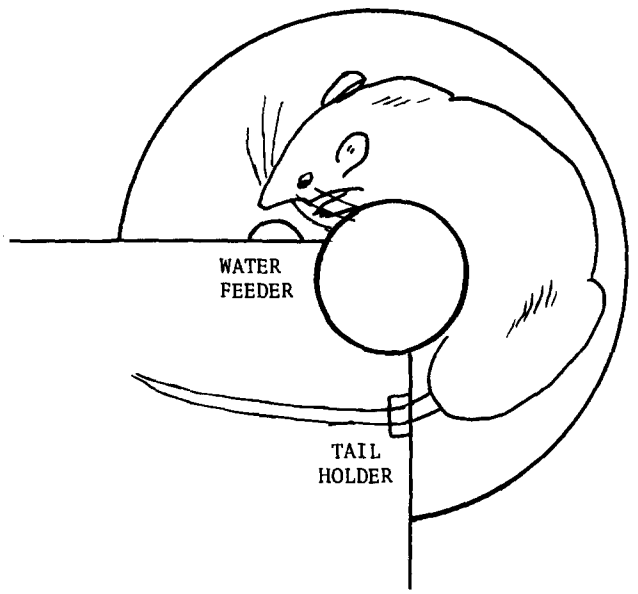

FIG. 1. Inplace circling apparatus. The location of the tail holder and the water feeder held the rat in an arched posture while running for water reinforcement. As the rat ran in place, the rotating turntable floor moved beneath him. With each 360 degree turn of the floor, the rat received a 0.05 ml drop of water.

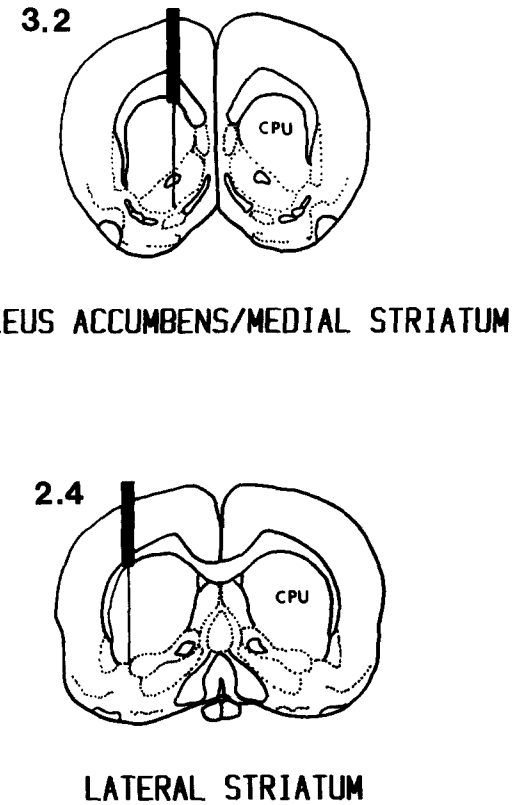

FIG. 2. Location of dialysis cannulae in the nucleus accumbens/medial striatum and lateral striatum. The entire vertical distance within striatum and nucleus accumbens was exposed to the dialysis membrane. Numbers refer to distance anterior to bregma in mm (12).

475 grams were used. They were individually housed and kept on a 12-hr light/dark cycle (lights on at 0600 hr). Food was freely available. Water deprivation was imposed as described below in the Procedure section.

Apparatus

The inplace circling apparatus (Fig. 1) was made of two concentric Plexiglas tubes, the outer 8″ and the inner 2″ in diameter. The rats ran in the circular path between the two cylinders. One quarter of the chamber was closed off to the rat and contained a tail-holding device. The floor was a turntable which was detached from the rest of the chamber and which rotated freely as a result of the rat's movements. Magnets attached to the disk triggered a detector linked to a Commodore 64 microcomputer to monitor rotations and administer a water reinforcer. The water-deprived rat was placed in the chamber with its tail held by a 3.5 cm piece of flexible rubber tubing. As the animal ran in place, the floor moved under him. Because of the locations of the tail holder and water feeder, an asymmetric arched posture was maintained by the rat. The rat received a 0.05 ml drop of water for each 360 degree turn of the floor disk. The apparatus was designed so that the rat could circle both to the right and to the left.

Surgery

After preoperative training (see below), the rats were divided into two groups, one receiving guide cannulae above nucleus accumbens/medial anterior striatum (NA/MS; n = 10), and the other receiving guide cannulae above the lateral anterior striatum (LS; n = 10). Guide cannulae consisted of 17-gauge stainless steel tubes (12 mm long) press fitted into the center of a 6 pin pedestal mount made by Plastic Products (Part MS363).

The rats were anesthetized using 150 mg/kg chloral hydrate and 20 mg/kg ketamine with 0.01 mg atropine sulphate. A David Kopf stereotaxic instrument was used and coordinates were taken from Pellegrino *et al.* (12), nosebar +5.0 mm. Coordinates for the NA/MS guide cannula were: anterior, 3.2 mm anterior to bregma, lateral 2.0 mm to the right of the midline, vertical 3.5 mm below the dura. Coordinates for the LS guide cannula were: anterior +2.2 mm, lateral 3.7 mm, vertical 3.0 mm (see Fig. 2). The dialysis cannula, when lowered, dialyzed a vertical column 4.5 mm in length below the guide in both brain regions.

Dialysis System

Dialysis cannulae were made from 320 μm diameter regenerated cellulose dialysis fiber (ENKA) with 50 μm i.d. fused silica inflow and outflow tubes. The tip of the dialysis fiber and the dialysis fiber/fused silica joint were sealed with epoxy. A 27 mm length of 21-gauge stainless steel tubing provided external support for the inflow and outflow tubes. The cannula was then cemented into the center of a plastic 6 pin electrode plug (Plastic Products, Inc., part 363). When the dialysis probe was placed in the previously implanted guide cannula, the screw-on cap and 5 remaining pins on the plug provided a secure hold for the device. Just before this plug was cemented into place, the inflow and outflow tubes were bent back so they would project toward the rat's tail to reduce interference with head movement and drinking. Twenty-four-gauge stainless steel sleeves were glued over the inflow and outflow tubes (see Fig. 3). The cannula inflow tube was connected via plastic tubing to a 1 ml syringe. The syringe was driven by an infusion pump (Harvard Apparatus, model 919) to perfuse the cannula at 0.39 μl/min. The perfusion fluid was

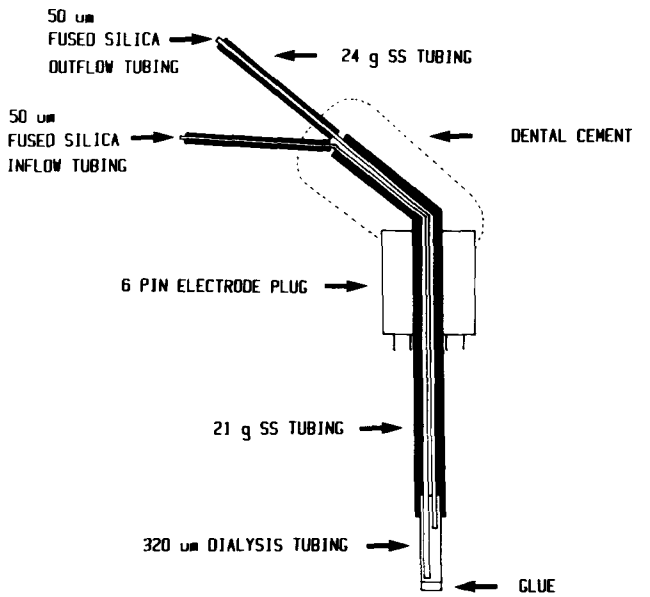

FIG. 3. Details of construction of the in vivo dialysis cannula.

Ringer's solution. The cannula outflow tube was connected via stainless steel tubing directly to an HPLC injector valve. The connecting tubing was 33 gauge to provide a low dead volume of 5 μl for a 60 cm length of tubing. In all results, the sample times were corrected for this tubing dead volume. The thin stainless steel tubing was protected by flexible plastic tubing. The dialysate was analyzed on line by an automated HPLC-EC system as previously described (15).

Chromatographic Conditions

Chromatographic equipment for analysis of the brain dialysate consisted of the following: An ISCO syringe HPLC pump (model μLC-500), a pneumatically operated Rheodyne injection valve (model 7413) with a 5 μl sample loop, a 100 mm × 1 mm reverse phase microbore column with 3 μm C18 Spherisorb packing (Keystone Scientific), a BAS LC-4B amperometric detector and a glassy carbon electrode with an applied potential of 0.7 V. The mobile phase was 0.05 M trichloroacetic acid, 0.2 M H_3PO_4, 0.1 mM EDTA, 0.22 mM sodium octyl sulfate, 2% methanol, at pH = 4.2 (1). The dialysate was automatically injected onto the column every 10 min (trained turning rats) or 20 min (free-drink/control rats) using a pneumatically activated valve controlled by a VIC 20 microcomputer (15).

Procedure

Ten rats (5 NA/MS and 5 LS) were trained to turn in both directions in the inplace circling apparatus described above. Prior to the initial training session, the rats were water deprived. They were rewarded with tap water. A total of 8 to 10 pre- and postoperative training sessions were conducted. On the first day of training most rats learned to run in place for water on their own. Minimal shaping was used as needed. Subsequent training sessions lasted 24 min. Rats satiated during this time and were given no additional water in their home cages. All deprived rats were given 16 hours continuous access to water once a week. The rats were trained for 3 to 5 days before surgery. The guide cannulae were then implanted as described above. After a week of recovery, water deprivation was again imposed (15-min access to water/day). Three to seven days of postoperative training were then conducted. During this time the rats were trained with a cable attached to their heads, simulating dialysis conditions.

After the final training session, a dialysis probe was lowered into the brain through the guide cannula under ether anesthesia. This cannula remained in place for all subsequent testing over several days. One practice dialysis session and two dialysis test sessions occurred over the next three days. All rats were dialyzed while turning in both directions. Half of the rats were first tested in the direction contralateral to the cannula, and the other half were first tested in the direction ipsilateral to the cannula. Before being placed in the inplace turning apparatus, animals were put into an 8 inch by 15 inch cylinder with a fixed floor and with no water available. Baseline dialysis measurements of dopamine and DOPAC were made in this chamber until stable trend lines were obtained up to four hours. The final 90 minutes of this period were used as a baseline to gauge behaviorally induced release of dopamine and DOPAC as described in the Data Analysis section below. The animals were then transferred to the inplace turning apparatus for a 24-min period of circling for water. They were then transferred back to the baseline chamber.

An additional 10 rats (5 NA/MS and 5 LS) were tested in free-drink and control conditions. These rats received no preoperative deprivation or training. A water deprivation schedule was imposed on the rats beginning three to five days after surgery. During this time, they were given 15-min access to water daily. Rats were on this deprivation schedule for a minimum of four days before testing.

The day prior to the first dialysis test day, the dialysis cannula was lowered into the guide cannula under ether anesthesia. The next day, after collection of baseline samples, the rats were either given access to water for 24 min, or were given no intervention (control). The opposite condition was run on the following day. Four of five rats in the NA/MS group were given their control session first; three of five rats in the LS group were given their control session first.

For the free-drinking animals, the entire dialysis sessions took place in the 8″ × 15″ baseline cylinder. During the 24-min drinking period, a water bottle was attached to the side of the cylinder.

After completion of testing, the animals were sacrificed and their brains were removed for histological verification of cannulae locations.

Histology

The animals were sacrificed with an overdose of chloral hydrate and were perfused with 10% formalin via intracardiac perfusion. The brains were removed and stored in 10% formalin for a minimum of one week. Cannula position was verified on thionin-stained sections.

Data Analysis

During baseline dialysis periods, DOPAC and dopamine concentrations systematically changed. In most animals, there was a gradual increase in dopamine concentrations and a decrease in DOPAC over the 90-min baseline session. For this reason, the baseline data points for both dopamine and DOPAC were fitted to straight lines by a linear least squares technique. Data obtained during behavioral intervention were expressed as percent deviation from the predicted line.

One-way analysis of variance was performed on the data; the Dunnett test was used for post hoc analysis.

RESULTS

Control Release of Dopamine and DOPAC

In animals maintained in the baseline drum for 160 minutes

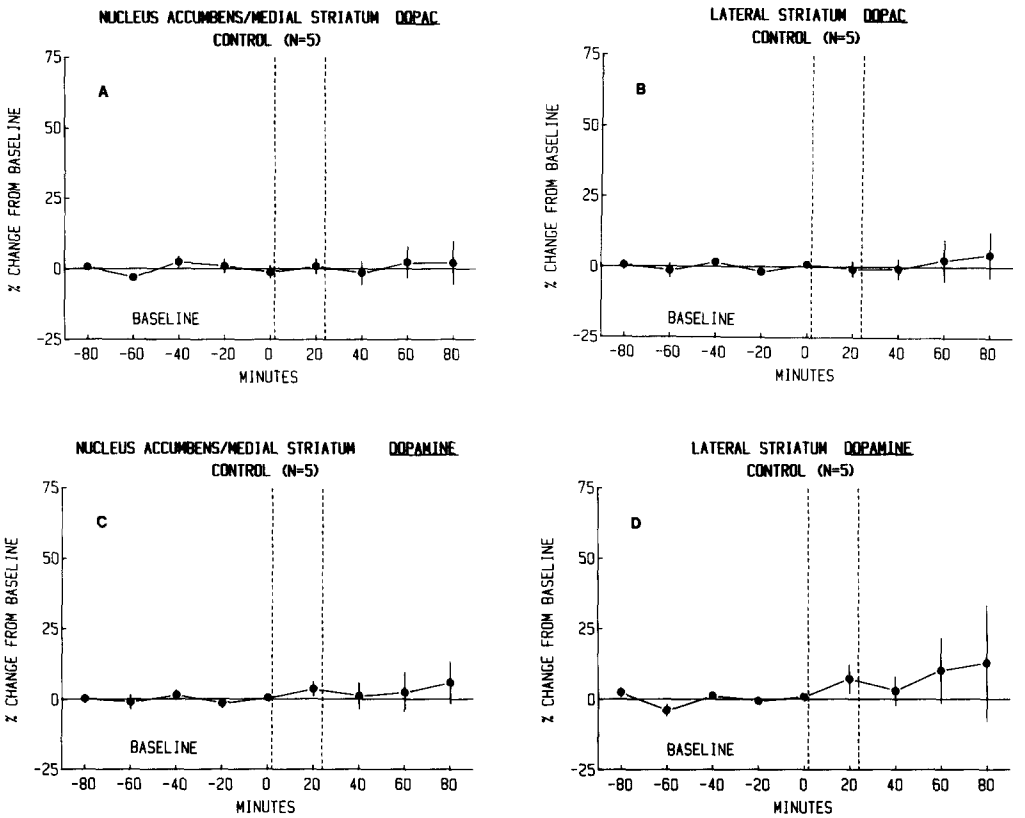

FIG. 4. Control release of dopamine and DOPAC from lateral striatum and nucleus accumbens. Because dopamine and DOPAC concentrations systematically changed during the first 90 minutes of sample collection, data were normalized to regression lines generated by that 90-minute baseline. Although data showed some increase in variability in the postbaseline phase, there was no significant deviation from the predicted line.

without water reward or without circling, there was no change in DOPAC or dopamine except for the systematic drift noted above (see Fig. 4). Figure 4 shows that under control conditions NA/MS and LS DOPAC and dopamine did not significantly diverge from the predicted baseline. There was a small tendency for LS dopamine to increase both in percent change from baseline and in variability as the session progressed (Fig. 4D).

Release With Trained Turning

Animals with cannulae in nucleus accumbens/medial striatum turned an average of 13 rpm during 24-minute test sessions both contralateral and ipsilateral to the side of the cannula while consuming an average of 16 ml of water. As shown in Fig. 5A and B, there was a significant contralateral and ipsilateral increase in DOPAC in this brain region [contralateral $F(8,32)=3.68$, $p<0.01$] [ipsilateral $F(8,32)=2.43$, $p<0.05$]. Post hoc analysis showed this increase persisted up to 80 minutes past the onset of turning. Figure 5C and D show that NA/MS dopamine did not significantly change during circling.

Animals with lateral striatal cannulae circled at 10–11 rpm and consumed 12–13 ml during the circling session. Inplace turning led to a pattern of results similar to those seen in nucleus accumbens/medial striatum. There were significant contralateral, $F(8,32)=3.98$, $p<0.01$, and ipsilateral, $F(8,32)=6.46$, $p<0.0001$, increases in DOPAC (see Fig. 6A and B). Post hoc analysis again showed this increase to be significantly different from baseline up to 80 min past the onset of turning. As shown in Fig. 6C and D, there were no significant changes in LS dopamine. Although there was a trend toward a late increase in dopamine concentration contralateral to the circling direction, these data were quite variable and results did not reach significance.

Release With Free Drinking

During the 24-minute free-drink period, all rats drank an average of 14–15 ml of water. As shown in Fig. 7A and B, free drinking led to a significant increase in DOPAC concentration in NA/MS, $F(4,15)=23.98$, $p<0.01$, and LS, $F(4,16)=6.56$, $p<0.01$. Post hoc analysis showed that this increase was significantly different from baseline at 40–80 min after the onset of drinking in both sites. Figure 7C shows that NA/MS dopamine tended to rise in parallel with DOPAC after free drinking, however, these changes did not reach statistical significance. From Fig. 7D, it can be seen that LS dopamine concentration rose in parallel with DOPAC, $F(4,16)=3.71$, $p<0.05$, and was significantly different from baseline 60 and 80 minutes after the initiation of drinking. Animals were active during the free-drinking periods. Their activity levels were not objectively quantified.

Histological Analysis

The dialysis cannula sites for four of the five trained turning NA/MS rats were between 2.8 and 3.6 mm anterior to bregma, 2.0 mm lateral to midline, and with a vertical depth ranging from 7.7 to 9.2 mm below dura. One rat had a somewhat more posterior

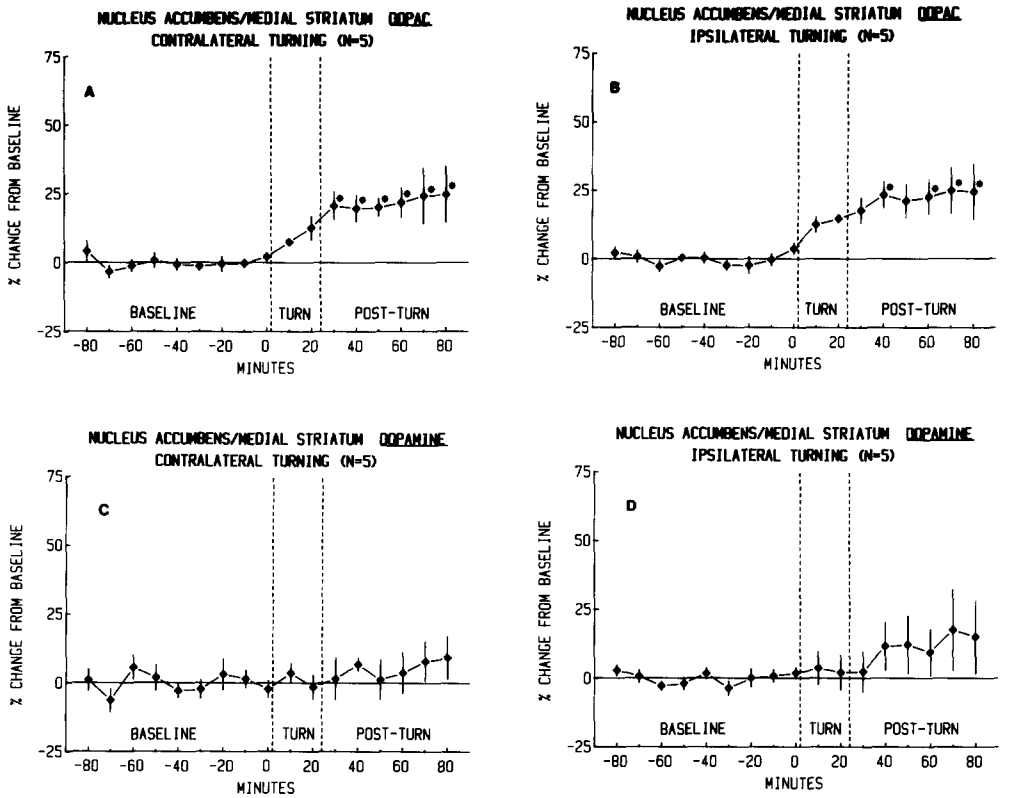

FIG. 5. Changes in dopamine and DOPAC release in nucleus accumbens/medial striatum during circling on a rotating disk treadmill. There was a significant increase in DOPAC release both contralateral and ipsilateral to the circling direction (*significantly different from last baseline point, $p<0.05$). There was no significant change in dopamine release. The increase in DOPAC persisted for at least one hour after the termination of circling.

placement, 2.0 mm anterior to bregma, 2.0 mm lateral to midline, and 7.7 mm below dura. The dialysis cannula placement for the LS trained turning rats ranged from 2.0 to 3.2 mm anterior to bregma, 3.0 to 3.8 mm lateral to midline, and 6.4 to 8.2 mm below dura.

The dialysis cannula placement for the NA/MS free-drink/baseline rats ranged from 2.8 to 3.2 mm anterior to bregma, 2.0 to 2.5 mm lateral to midline, and 7.5 to 9.5 mm below dura. The dialysis cannula placement for the LS free-drinking rats ranged from 1.6 to 3.0 mm anterior to bregma, 3.5 to 4.5 mm lateral to midline, and 7.0 to 9.5 mm below dura.

DISCUSSION

We have observed a bilateral increase in DOPAC release from n. accumbens/medial striatum and lateral striatum during running on a rotating disk. Similar increases in DOPAC were seen when untrained water deprived animals were given 24 minutes access to water.

The bilateral increase in nucleus accumbens/medial striatal DOPAC while animals ran in place is consistent with the hypothesis that nucleus accumbens is important in locomotor behavior (8,13) or speed of movement (6). There was no lateralization of nucleus accumbens dopamine or DOPAC release as might have been predicted from the tissue concentration changes seen previously during trained circling in space or forced circling on a rotating disk (6,23).

The bilateral increase in lateral striatal DOPAC is different from the electrochemical results of Yamamoto, Lane and Freed (21). This previous report from our lab showed a 33% increase in the contralateral/ipsilateral catechol release ratio as a result of trained turning. With the present dialysis experiments, there was a late increasing trend in extracellular fluid dopamine contralateral to the circling direction. However, there was large variability in the data, and these results did not reach statistical significance. In addition, Fig. 4 shows that even under control conditions, there was a tendency for LS dopamine to increase and become more variable. The bilateral increase in LS DOPAC indicates that dopaminergic activity increases bilaterally in this model of circling.

The reason for the discrepancy between the present results and those previously obtained in our laboratory remains unclear. It could be due to several factors. First, the inplace circling task is different from the original trained turning task since the animal is not moving through space but simply maintains a curved body arc. This is an unlikely explanation since lateralization by tissue assay measurement was found using a forced circular treadmill, in an apparatus somewhat similar to the one used in this study (6). In that previous experiment, the rat did not move through 360 degrees of space but the floor was forcibly moved beneath it by an electric motor. In that experiment, maximum laterality in striatum was seen in a cylinder 4.7 inches in diameter rather than 8 inches as in the present experiment. The body arc maintained in the smaller cylinder was somewhat more extreme than in the present device although in the prior study, laterality was seen in nucleus accumbens with a moderate body arc. A major difference between the original study of Yamamoto, Lane and Freed (21) and the present study is the neurochemical measurement technique: in vivo electrochemistry recorded bilaterally and simultaneously as op-

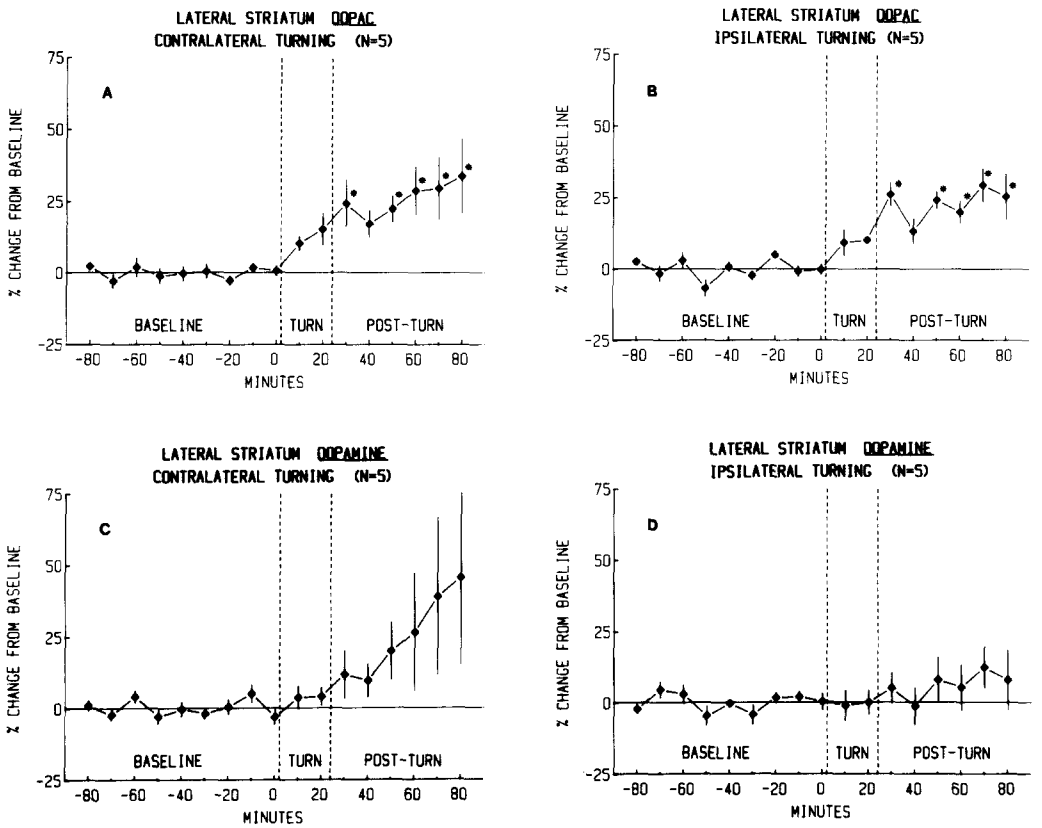

FIG. 6. Lateral striatal dopamine and DOPAC release during circling on a rotating disk treadmill. As in Fig. 5, there was a significant increase in DOPAC bilaterally (*significantly different from last baseline point, $p<0.05$). There was a trend towards increased contralateral dopamine release; however, this did not reach statistical significance.

posed to in vivo dialysis performed sequentially.

Since we devised the trained circling rat model (22), several groups have used variations of it to test the relationship between movement and dopamine activation. In tissue assay experiments with circling rats trained on an FR2 schedule, Szostak *et al.* (19) reported a bilateral increase in homovanilic acid (HVA) to dopamine ratios in striatum and bilateral increases in HVA and HVA to dopamine ratios in nucleus accumbens. They did not find changes in tissue dopamine or DOPAC. Also using our circling rat model, Schwarting and Huston (17) found bilateral increases in DOPAC and HVA in dorsal striatum, and bilateral increases in DOPAC to dopamine ratios and HVA to dopamine ratios in both dorsal and ventral striatum. In neither of these papers was the increase in dopaminergic activity lateralized.

As a followup to the forced circling experiment previously described (6), our laboratory has studied the electrophysiology of dopamine cell firing during movement. Diana *et al.* (5) found bilateral activation of dopaminergic neurons in the substantia nigra pars compacta in rats forced to run on a circular treadmill. Thus, in this electrophysiological experiment (5) and the two tissue assay experiments discussed above (17,18), bilateral increases in dopaminergic activity were observed with turning behavior. These results are all consistent with the bilateral increases in DOPAC found with inplace turning reported here.

Free drinking led to a significant increase in DOPAC in nucleus accumbens/medial striatum and in lateral striatum; and to an increase in lateral striatal dopamine. This result is consistent with that of Schwarting and Huston (17). They noted increased DOPAC to dopamine ratios in untrained water deprived animals given 15 minutes access to water. Chang *et al.* (3) reported a 40% increase in nucleus accumbens dopamine release in water deprived rats after free access to water. While the increased DOPAC release we have seen suggests increased dopaminergic activity, we did not measure an increase in extracellular fluid dopamine in the accumbens. On the other hand, we did find increased dopamine release in lateral striatum. The magnitude of this change was not large. A comparison of Figs. 4D and 7D shows that while LS dopamine is significantly increased with drinking compared to baseline, control dopamine is not increased because the data are more variable. However, the mean values for dopamine under these two conditions are equivalent. Thus, larger sample sizes than $n=5$ are necessary to detect 10% differences in dopamine release.

The increase in NA/MS and lateral striatum DOPAC seen with free drinking is similar in magnitude to that seen with the water rewarded inplace turning task. These equivalent increases in DOPAC seen in the trained-turning and free-drink paradigms suggest that the turning task is not unique in being able to elicit changes in dopamine activity in NA/MS and LS. Thus, in the present experiments, we cannot say whether changes in DOPAC release were due to motor activity, the act of drinking, or the amount of fluid consumed. In a subsequent experiment, we have found that animals with low water consumption but a high level of activity show changes in DOPAC release similar to animals with high water consumption and high activity, suggesting that it is activity rather than volume of water consumed that is related to activation of dopaminergic systems (16).

Another possible explanation for the increase in DOPAC with trained turning is tail pinch-induced stress. Dopaminergic involvement has been demonstrated in tail pinch and other stress situations (4, 9, 18). The animals in the turning apparatus have their tails

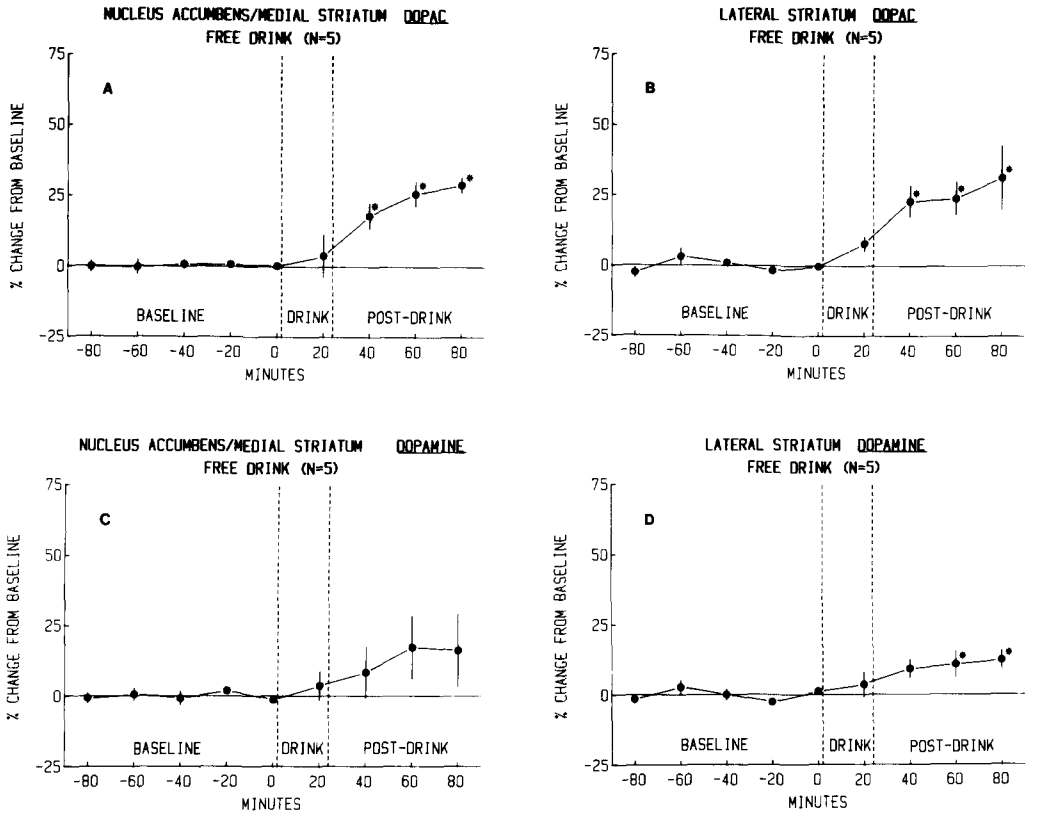

FIG. 7. Dopamine and DOPAC release from nucleus accumbens/medial striatum and lateral striatum during free drinking. Both regions showed a significant increase in DOPAC release in the 60 minutes following the termination of drinking. In both regions, there was a tendency for dopamine to increase which reached statistical significance in lateral striatum.

held by a piece of rubber tubing to keep them oriented appropriately. While either the circling activity or the tail pinch could have led to increased DOPAC release, neither condition was present in the free-drinking experiment. Thus, increased dopaminergic activity is likely to occur under a variety of behavioral circumstances.

In both the circling and free-drinking experiments, DOPAC was increased and yet dopamine itself was only increased in one site (lateral striatum) under one condition (free drinking). Since DOPAC is a metabolite of dopamine these results appear inconsistent. An explanation for this discrepancy may exist with the dopamine reuptake mechanism. Using in vivo voltammetry, Michael *et al.* (10) showed that 10 sec of medial forebrain bundle electrical stimulation led to apparent dopamine release which peaked 20 sec after stimulus onset and returned to near baseline levels within one minute. These results indicate that there are rapid elimination mechanisms which remove dopamine from the synapse soon after release, making it difficult to track changes with the present dialysis technique. DOPAC has been used to estimate changes in dopamine release. Using tissue assay and pharmacological techniques, Roth *et al.* (14) argue that changes in DOPAC levels reflect changes in impulse flow in dopamine neurons. Thus, while increased dopamine release may be masked by the reuptake mechanism, release may be reflected by an increase in DOPAC output.

An alternative interpretation is found in a hypothesis presented by Imperato and DiChiara (7). These authors argue that DOPAC and HVA production are indicators of dopamine synthesis while dopamine release is an indicator of dopamine cell firing. This hypothesis suggests that the effects of circling and drinking behavior on the dopamine system we have observed are due to an increase in dopamine synthesis but not in the firing rate of dopaminergic cells. However, our laboratory has measured increased dopamine cell firing when animals run on a rotating disk (5). Because synaptic release of dopamine cannot be directly measured, there is no absolute way of resolving the relationship between synaptic dopamine release and changes in extracellular DOPAC concentration. Nonetheless, it is likely that the increases we have seen in DOPAC during trained turning and free drinking reflect activation of brain dopamine systems.

ACKNOWLEDGEMENTS

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