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Striatal Dopamine Activity and Unilateral Barpressing in Rats

WILLIAM H. CHURCH, KAREN E. SABOL,* JOSEPH B. JUSTICE, JR.[1] AND DARRYL B. NEILL*

Departments of Chemistry and Psychology, Emory University, Atlanta, GA 30322*

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CHURCH, W. H., K. E. SABOL, J. B. JUSTICE, JR. AND D. B. NEILL. *Striatal dopamine activity and unilateral barpressing in rats.* PHARMACOL BIOCHEM BEHAV 25(4) 865–871, 1986.—A micro-punch tissue assay was used to measure changes in dopamine content at twenty-six sites within the striatum of rats trained to barpress exclusively with one forepaw for food pellets. Analysis of dopamine (DA) and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), was carried out using HPLC with electrochemical detection. The barpress group had a significantly higher DOPAC/DA ratio in both the contralateral and ipsilateral hemispheres when compared to feeding and homecage controls. The DOPAC/DA ratio is considered to be a measure of dopaminergic neuronal activity, thus suggesting a bilateral activation of the neostriatal dopaminergic afferents as a result of the motor performance. Topographical analysis within the barpress group revealed an anterior-posterior, medial-lateral gradient of dopaminergic activity with the posterior and lateral sites showing the greatest increases over the controls. The results of this experiment indicate that localized changes in neuronal activity can be monitored with the micro-punch assay-HPLC/EC technique and that voluntary motor behavior produces an activation of the striatal dopamine system.

Nigrostriatal dopamine Unilateral barpress HPLC/EC Micro-punch

THE idea of a role of neostriatal (caudate/putamen) dopamine in sensorimotor function has come from clinical and experimental evidence. The experimental evidence has primarily consisted of animals exhibiting impaired sensorimotor function after damage to the nigrostriatal dopamine pathway. In particular, unilateral damage to this pathway results in lateralized sensorimotor dysfunctions for many [8, 18, 29] or restricted regions of the body [19].

At the neuronal level, recent interpretations of the effect of dopamine on striatal cells [23, 26, 34] have emphasized how dopamine may play a "permissive" role; i.e., dopamine may not be used to transmit information but may bias the reactivity of striatal neurons to other neurotransmitters being released by other striatal afferents.

If dopamine is playing a permissive role in striatal functioning, is dopamine release increased during behavior, or does it stay relatively constant? The most direct way of approaching this question is to measure dopamine release as a consequence of behavior. A few studies [9, 13, 14] have shown that rats barpressing for water show increased striatal dopamine metabolism. Of particular interest, rats trained to rotate show increased dopamine release restricted to the striatum contralateral to the direction of rotation [31–33].

In the following study, we examined the question of whether a unilateral increase in dopamine release could be produced by training a rat to barpress with one paw. Unilateral striatal dopamine loss in rats has been shown to produce impairments in the use of the contralateral paw [27,30], and unilateral electrolytic lesions of the striatum result in deficits in barpressing with the contralateral paw [11].

In addition to determining if a unilateral change in dopamine release could be produced by unilateral barpressing, we were also interested in the possibility that this change would be restricted to a particular striatal subregion. Studies manipulating striatal dopamine and measuring the behavioral effects have shown the existence of functionally different striatal subregions [7, 8, 21, 22]. In a recent study [27], we found that performance of a unilateral forepaw food retrieval task was impaired by dopamine loss in lateral neostriatum. We wondered if the same striatal subregion would uniquely show increased dopamine release as a result of unilateral barpressing.

We used the ratio of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) to dopamine (DA) in striatal tissue samples as an index of dopamine release. This measure has been used in studies of drug effects on [15], and behavioral correlates of [12] dopamine release.

METHOD

Animals

Eighteen male Sprague-Dawley rats (Harlan/Sprague-Dawley, Indianapolis, IN) weighing 300–350 grams before food deprivation were used. The animals were housed individually in a colony on a 12 hr lighting cycle (lights on 0800

[1]Requests for reprints should be addressed to Dr. J. B. Justice, Jr., Department of Chemistry, Emory University, 1515 Pierce Drive, Atlanta, GA 30322.

hr). The barpress and feeding control animals were maintained at 85% of their free-feeding weight. Water was freely available to all groups.

Procedure

Paw preference determination. Paw preference was established prior to barpress training using a food-retrieval apparatus previously described [27]. The rat was placed in a chamber which had ten slots in the wall of one side. Within each slot, resting on a shelf separated from the apparatus by a gap, was a 45 mg BioServ pellet (Frenchtown, NJ). The width and depth of the slot prevented the rat from retrieving the pellet with either tongue or both forepaws; only one forepaw could be used to grasp the pellet and carry it over the gap. Training began after two days of habituation exposure to the chamber. Training consisted of four trials/day, 10 pellets/trial, for four days. Each trial lasted until all ten pellets were no longer available to the rat (successfully retrieved or lost) or 5 minutes had elapsed. The total number of attempts with each paw was recorded for the four days to determine the degree of paw preference. A rat was classified as having a unilateral preference if one paw was used on 75–100% of the attempts, and as ambidextrous if one paw was used on 50–74% of the attempts. Paw preference was usuually apparent on the first training day.

The animals were then assigned to three groups: (1) homecage control (HC), (2) feeding control (FC), and (3) barpress (BP). The feeding control group served as a yoked control. We attempted to distribute the animals with left, right, and ambidextrous paw preferences across the three groups.

Barpress training. Training sessions began 1 hr into the light cycle and were 30 minutes in duration. The apparatus consisted of a 30×30×45 cm aluminum and Plexiglas test chamber enclosed in a plywood shell. Food (45 mg BioServe pellets) was delivered to a receptacle mounted on the chamber wall. The response bar could be positioned at various heights above and below the level of the chamber floor by adjusting the height of the floor. When positioned below floor level, the bar could only be reached via a slot cut into the floor next to a wall of the chamber. The rat was forced to use the right forelimb to barpress by opening the slot next to the right wall, or the left forelimb by opening the left slot. The particular slot used was determined based on the paw preference of the individual animal. Slot width could also be adjusted to further limit use to one forelimb.

Initially, the animals were trained on a continuous reinforcement schedule (CRF) with the bar located above the floor level. After the animals began to respond regularly, the bar was positioned even with the floor level, and then below floor level. Once adequate performance was achieved on the CRF schedule with the bar below the floor level, a fixed ratio schedule was implemented. The ratio value was adjusted in increments of 5 every third session until a FR-20 schedule was in place. The rats were then tested daily until they performed on the FR-20 schedule with total responses for the 30 minute session not varying more than 25 percent over 7 sessions. The average total responses for each of six animals was approximately 1300 per session.

Feeding control animals were placed into a chamber next to the barpress chamber. Their chamber had a food pellet receptacle but no bar. Every time the barpress animal received a pellet as a consequence of barpressing, the matched feeding control animal received a pellet.

Homecage controls simply lived in their cages for the duration on the barpressing experiment.

Assay procedure. A barpress rat, the matched feeding control, and homecage control constituted a triad. Assays were always conducted by triads to lessen the effect of any differences between assay runs on different days. Assays were performed every other day; the sequence was homecage control-feeding control-barpresser. The day of their assay a barpress or feeding control animal was removed from the chamber twenty minutes into the session. The animal was immediately placed into a glass chamber saturated with chloroform for 30 seconds. The animal was then decapitated and the brain removed from the skull. After the brain was blocked in the angle of the stereotaxic atlas [24] used for neuroanatomical landmarks, it was placed on a glass slide and frozen in powdered dry ice. The time between decapitation and placement of the brain in dry ice was less than 3 minutes for all animals so as to lessen any post-mortem changes in neurotransmitter content.

The frozen brain was mounted on the stage of a freezing microtome and beginning at AP level 9.0, four 1 mm-thick slices were cut and kept frozen using a cold plate. Neostriatal tissue was removed from each slice using a 1.5 mm stainless steel punch. As shown in Fig. 1, 26 punches were taken throughout the neostriatum, 13 punches in each hemisphere. Individual punches were placed in polyethylene microcentrifuge tubes containing 500 μl of 10% trichloroacetic acid and an internal standard. The punches were then sonicated and the tissue debris separated out by centrifugation at 3000 × g for 10 min.

Tissue dopamine and DOPAC content were determined in each punch using HPLC with electrochemical detection [28]. The HPLC system consisted of a Varian Series 5000 pump, a Waters μBondapak C-18 column (3.9 mm × 30 cm), and a glassy carbon working electrode (BioAnalytical Systems, West Lafayette, IN). An LC-3 potentiostat (BAS) was used to maintain a potential of +0.62 V vs. an Ag/AgCl reference electrode. The mobile phase consisted of 0.02 M sodium phosphate monobasic made acidic (pH=3.2) with HCl and containing 0.25 mM sodium hexyl sulphate as an ion-pairing agent. All solutions were HPLC grade and were filtered and degassed with helium before use. The mobile phase flow rate was 1.8 ml/min and a 100 μl sample loop was used.

Calibration curves were constructed prior to and after each day's analysis. The solutions for the calibration curves were prepared daily using a 0.1 g/l stock solution containing 0.1% sodium metabisulfite and 0.01 M HCl. 3,4-Dihydroxybenzylamine hydrobromide (DHBA) was used as an internal standard.

Protein content of each punch was determined using the assay of Lowry *et al.* [17].

Data analysis. Dopamine and DOPAC values were expressed as ng/mg protein. Comparisons of group and site means were carried out using 2-way analysis of variance (ANOVA). If significance was observed with the ANOVA, Scheffe's multiple contrasts test was applied to compare means.

RESULTS

To determine if a unilateral change in dopaminergic transmission was associated with the unilateral barpressing behavior, tissue levels of DA and DOPAC and the DOPAC/DA ratio for the striatal sites contralateral to the limb used for barpressing were expressed as a fraction of

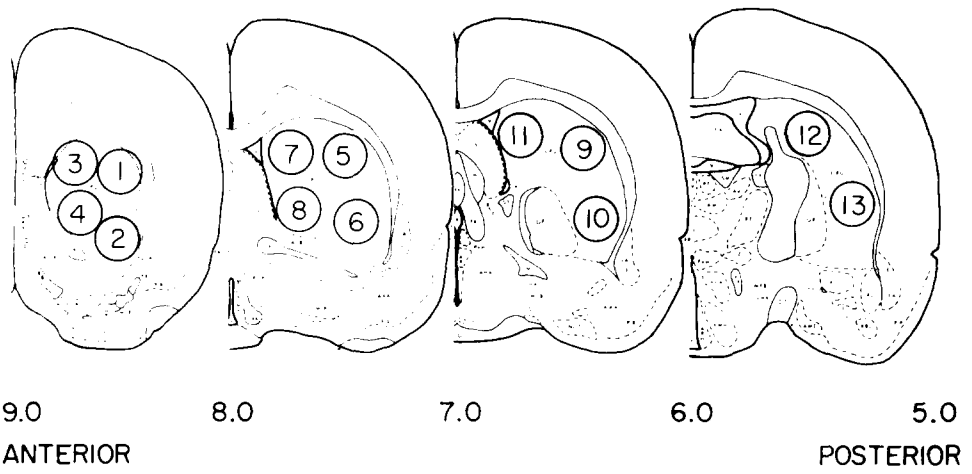

FIG. 1. Anatomical representation of punch locations. Anterior-posterior scale from Pellegrino *et al.* Tissue slices were 1 mm thick.

those for the ipsilateral sites. Examined across groups and sites by analysis of variance, no statistically significant effect was found for DA, DOPAC, or the DOPAC/DA ratio.

While a unilateral effect was not found, Fig. 2 indicates that a bilateral change in dopamine release was associated with barpressing. The barpress group showed a significant increase in the DOPAC/DA ratio values in both hemispheres over the homecage control and the feeding control groups (overall contralateral, $F(2,219)=20.47$, $p<0.0001$; overall ipsilateral, $F(2,219)=16.41$, $p<0.0001$; barpress group different from both homecage and feeding controls $p<0.05$ for each hemisphere). This effect can be largely attributed to an increase in DOPAC levels. The contralateral DOPAC level of the barpress group was significantly elevated over that of the homecage control group (overall, $F(2,219)=7.70$, $p<0.0006$; $p<0.05$ compared to homecage). There was no significant effect in the ipsilateral hemisphere (overall, $F(2,219)=2.57$, $p<0.08$). DOPAC levels in the barpress group tended to be higher than those of the feeding control but were not significant. A small but statistically nonsignificant decrease in the DA level was also seen in both hemispheres of the barpress group. The feeding control group showed a significant increase in the DOPAC/DA ratio in the contralateral hemisphere when compared to the homecage control group ($p<0.05$ by Scheffe's test) but no similar increase was seen in the ipsilateral hemisphere ratio level.

To determine if the bilateral increase in dopamine release in the barpress group was localized to certain regions within the striatum, a comparison of site means within each hemisphere was carried out across the three groups. Table 1 lists the individual means calculated for DA and DOPAC in each punch site. While no site differences were noted for DA or DOPAC levels, the barpress group's DOPAC/DA ratio values in sites 12 and 13 were significantly elevated in both the contralateral and ipsilateral hemispheres (see Fig. 3).

Figure 3 illustrates the changes in the DOPAC/DA ratio for the feeding control group and the barpress group expressed as a percentage of the homecage control group. These percentages were computed for each feeding control and barpress animal by comparing individual ratio values for these groups with respect to those of the homecage

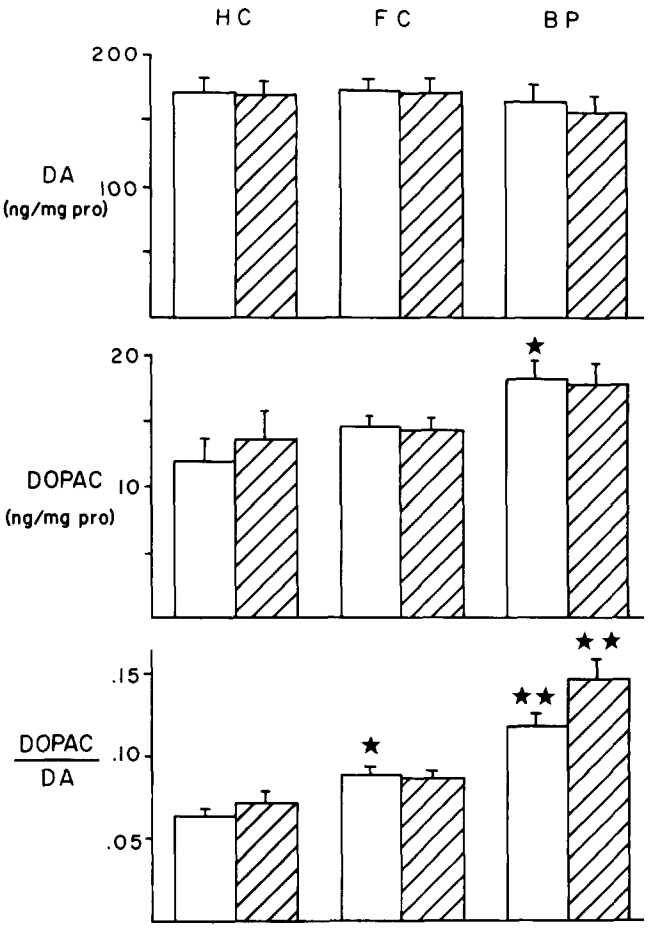

FIG. 2. Contralateral and ipsilateral hemispheric values of the neurochemical data for each group. Values represent the mean of 78 data points. Error bars represent SEMs. Open column: contralateral; striped column: ipsilateral. ★Indicates significant differences from homecage controls at $p<0.05$. ★★Indicates significant difference from homecage and feeding controls at $p<0.05$.

TABLE 1
NEUROCHEMICAL DATA FOR INDIVIDUAL PUNCH SITES

	Homecage Control		Feeding Control		Barpress	
Punch Site	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral
			DA			
1	280.1 (68.9)	195.9 (41.4)	233.7 (19.4)	242.9 (30.6)	195.3 (7.8)	200.0 (15.6)
2	184.3 (25.1)	192.0 (34.9)	205.6 (27.2)	212.8 (27.4)	162.3 (11.3)	174.2 (14.5)
3	232.6 (33.0)	251.6 (32.2)	252.0 (32.9)	266.9 (29.8)	219.2 (17.1)	221.4 (8.9)
4	153.1 (23.1)	152.8 (17.7)	170.0 (20.8)	166.5 (21.2)	142.6 (16.4)	123.5 (10.4)
5	249.6 (32.0)	273.5 (38.5)	255.6 (13.7)	265.1 (29.0)	235.0 (34.8)	275.9 (50.9)
6	186.0 (25.1)	214.8 (26.8)	188.1 (13.4)	203.6 (24.2)	202.0 (35.7)	184.7 (11.6)
7	248.9 (34.2)	237.9 (36.6)	246.0 (14.3)	251.4 (23.4)	233.1 (34.9)	229.9 (24.7)
8	131.4 (12.6)	143.1 (13.9)	132.4 (16.9)	134.6 (10.5)	123.9 (8.4)	108.1 (22.7)
9	190.6 (25.2)	185.2 (23.1)	177.0 (15.5)	164.0 (20.4)	186.7 (43.2)	188.5 (31.6)
10	140.5 (16.0)	131.2 (22.6)	130.7 (12.9)	114.3 (13.0)	153.1 (28.9)	106.8 (18.1)
11	191.0 (22.2)	186.8 (26.3)	209.9 (20.1)	181.7 (7.3)	201.0 (21.3)	173.7 (30.9)
12	79.4 (10.6)	89.0 (11.2)	76.0 (9.3)	71.8 (7.2)	64.4 (13.2)	49.8 (9.1)
13	70.7 (6.6)	70.6 (7.8)	69.5 (14.9)	53.9 (10.1)	54.8 (11.8)	34.4 (8.1)
			DOPAC			
1	16.0 (3.8)	11.4 (2.4)	16.4 (2.7)	19.4 (2.8)	18.5 (3.3)	21.5 (6.3)
2	13.4 (3.0)	20.0 (10.8)	20.9 (2.8)	22.4 (4.3)	19.5 (3.3)	27.1 (9.0)
3	20.1 (9.6)	24.8 (15.1)	22.1 (4.4)	17.6 (2.6)	20.6 (5.4)	21.7 (4.6)
4	14.7 (4.5)	20.4 (7.6)	18.8 (3.8)	19.3 (3.6)	24.2 (7.5)	19.7 (3.4)
5	14.0 (3.3)	15.3 (4.5)	14.1 (3.6)	16.6 (3.1)	24.1 (8.3)	29.0 (13.0)
6	10.6 (2.2)	13.4 (3.5)	14.8 (1.7)	15.8 (3.8)	22.8 (7.8)	17.2 (3.5)
7	18.3 (3.8)	16.7 (4.0)	17.0 (3.0)	16.2 (1.7)	20.6 (5.5)	21.8 (6.2)
8	11.8 (3.4)	13.4 (2.5)	14.7 (2.2)	14.2 (1.7)	18.6 (3.4)	14.6 (3.5)
9	10.0 (2.3)	9.4 (2.8)	11.1 (1.6)	10.0 (2.3)	16.2 (4.7)	14.9 (3.3)
10	7.5 (1.7)	8.7 (2.6)	10.5 (1.2)	7.8 (1.4)	13.9 (3.6)	11.7 (1.9)
11	10.0 (2.5)	10.4 (2.5)	12.2 (1.7)	9.2 (2.5)	18.0 (4.7)	12.9 (2.8)
12	5.2 (1.2)	7.0 (2.0)	6.1 (1.0)	5.9 (1.3)	9.2 (1.6)	7.7 (0.9)
13	4.9 (1.4)	7.1 (2.4)	7.65 (1.9)	7.8 (2.86)	6.8 (1.1)	9.0 (2.1)

Values represent the means calculated from 6 animals (SEM). Dopamine and DOPAC are expressed as ng/mg protein.

control animal in their triad. Inspection of this figure suggested a greater activation in the lateral portions of the striatum. This hypothesis was tested by combining the DOPAC/DA ratio values of the medial sites (punches 3, 4, 7, 8, 11) and lateral sites (punches 1, 2, 5, 6, 9, 10, 12, 13) and comparing these two values to the respective values in the homecage control group. Although the ANOVA failed to indicate any significant differences, the combined lateral sites of the contralateral hemisphere of the barpress group nearly attained statistical significance when compared to the contralateral hemisphere value of the homecage control group.

DISCUSSION

Striatal tissue samples taken immediately after rats had performed a barpress task using one paw showed no evidence of a unilateral increase of dopamine release as indicated by DOPAC/DA ratio values. Rather, the data indicated a bilateral increase in dopamine release. These results are surprising in light of the clearly unilateral behavioral deficits which follow unilateral striatal tissue damage [11] and dopamine loss [27,30], and the unilateral increase in dopamine release in rats trained to rotate [31,32].

Our finding of a bilateral activation could be a result of several factors. First, the present task may not have sufficiently restricted sensorimotor activity to one side of the body. Observations of the rats during performance of the task revealed that the ipsilateral forepaw was used for body support as the rat reached down into the slot to gain access to the bar. The posture which the rat had to assume in order to gain access to the bar appeared awkward and unnatural. An involvement of the striatum in postural maintenance has long been known so a bilateral activation may have resulted from bilateral posture changes. Second, the projection from sensorimotor cortex to neostriatum, unlike other components of the corticostriatal projection, is known to be bilateral; this part of cortex projects strongly to ipsilateral neostriatum and less strongly to contralateral neostriatum [2,4]. The corticostriatal projection might modulate striatal dopamine release [1,25]. However, we find it difficult, given the relatively weak nature of the contralateral projection, for this explanation to account for our strongly bilateral effects.

From studies on the effects of striatal manipulations on behavior, we expected to find changes in dopamine release which were most pronounced in small striatal subregions. Changes restricted to small subregions clearly did not occur. Our finding that the entire neostriatum, anterior to posterior, showed evidence of increased dopamine release can be viewed as consistent with our finding of bilateral activation.

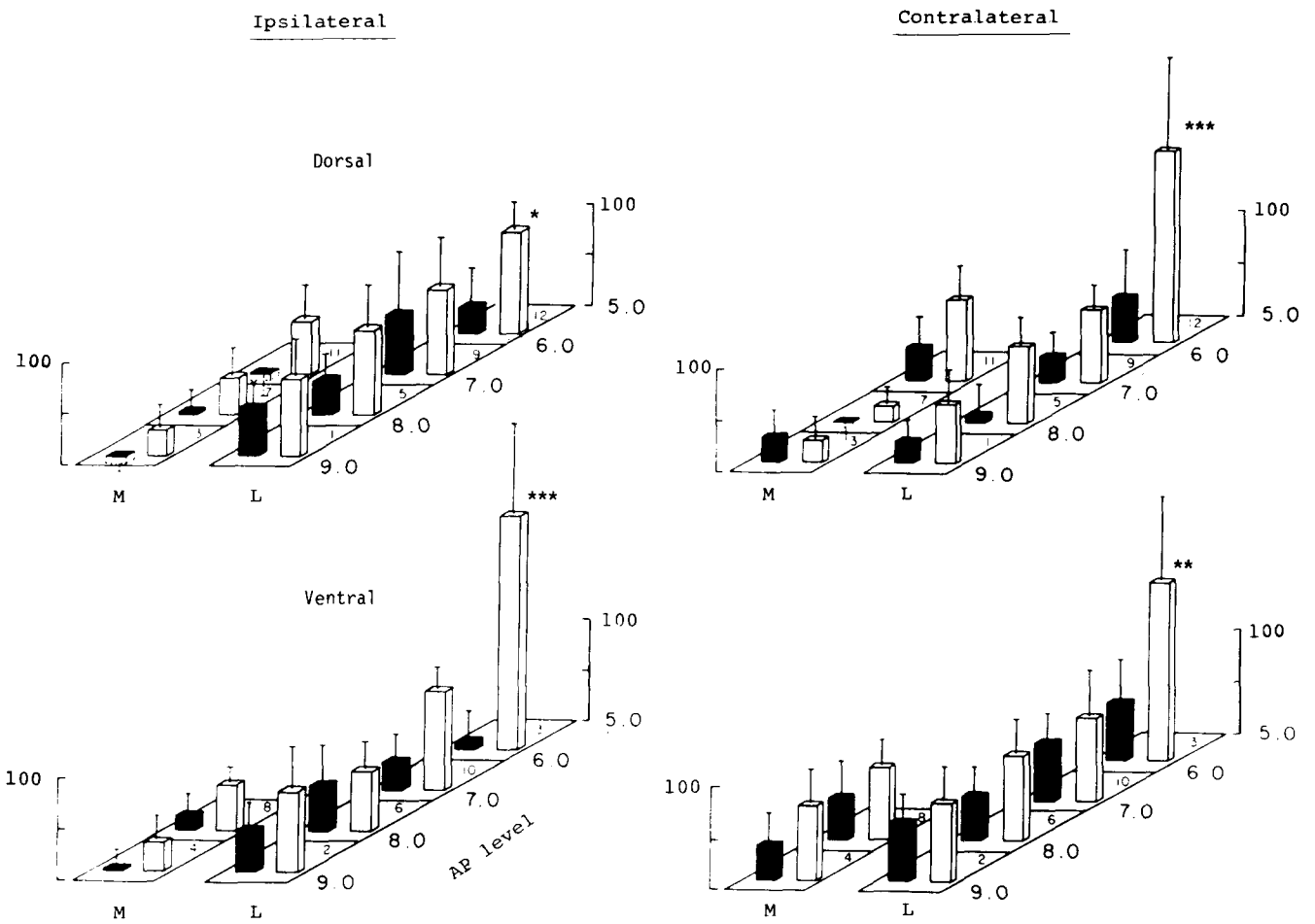

FIG. 3. Graphical representation of the mean increase in DOPAC/DA ratios over homecage controls for both the feeding control and the barpress groups. Scales represent a 100% increase. Values represent the mean increase at each site (N=6). Error bars represent SEMs. ★Indicates significant difference from homecage controls at $p<0.05$. ★★Indicates significant difference from homecage controls at $p<0.01$. ★★★Indicates significant difference from homecage controls and feeding controls at $p<0.05$.

A behavioral situation which evokes activation of much of the neostriatum might also tend to evoke bilateral activation.

We did, however, find evidence of a degree of subregional activation in that enhanced dopamine release was strongest in lateral neostriatum along the entire anteroposterior axis. Medial, particularly dorsomedial, neostriatum seemed to consistently show smaller increases in the DOPAC/DA ratio than lateral neostriatum along the entire extent of the structure. In addition, when portrayed as percentage change, the increase in DOPAC/DA ratio seemed to become stronger in an anteroposterior gradient across lateral striatum. Individual punch sites in posterolateral neostriatum were the only ones showing statistically significant changes as individual sites (see Fig. 3). In a 6-hydroxydopamine lesion study from our group [27], we found that impairments in a unilateral forelimb food retrieval task seemed most related to dopamine loss in lateral neostriatum, and the relationship became stronger with loss more posteriorly in the lateral striatum.

The relatively small increase in DOPAC/DA ratio in medial anterior neostriatum may relate to known functional aspects of this striatal zone. We [27] have found that dopamine loss in medial anterior neostriatum produces rotational movements. Nigral transplants which innervate this region [6], but not others [5], ameliorate the rotation resulting from unilateral dopamine loss throughout the neostriatum. In our barpressing task, the rat was constrained from rotating because he had to reach down into a slot to barpress, thus producing a weaker activation of the medial zone. We have found in rats trained to rotate unilateral activation of both medial and lateral neostriatum (unpublished results).

Lateral, particularly posterolateral, neostriatum in the rat may be functionally homologous to the putamen in the primate. Anatomically, rat lateral neostriatum [2,4], like primate putamen [16], receives the majority of its cortical afferents from sensorimotor cortex. In addition, several studies have shown that cell firing in the putamen of monkeys is closely correlated with contralateral limb movements [3].

Our experiment was motivated, in part, by the demonstration that rats trained to rotate show unilateral increases in synthesis (tyrosine hydroxylase activity [20]) and release (DOPAC [31,33]) of neostriatal dopamine. Our results were different not only in that we found a bilateral increase in dopamine activity, but that we did not observe any increase

in dopamine levels, which are thought to reflect the increased synthesis in the rotation paradigm [20,31]. Our finding of an increase in DOPAC without an increase in dopamine is consistent with previous work [13] using barpressing as the behavior.

One behavioral difference between the barpress task and the rotational task is that all of the reported barpress tasks have used periodic schedules of reinforcement such as the present FR-20. The rotational task, in contrast, uses continuous reinforcement (FR-1). A recent study from our group [10] using brain stimulation reward has found that rats barpressing on a FR-10 schedule show larger increases in the DOPAC/DA ratio than rats barpressing on a FR-1 schedule. One can speculate that periodic reinforcement *per se* enhances dopamine release, because we (Fig. 2) and Emmett-Oglesby *et al.* [9] found that the feeding (yoked) controls showed an increase in dopamine release. Such an effect might explain why bilateral activation occurs in the barpress task but not in the rotation task.

In conclusion, training rats to barpress with one paw by the method we have used seems to bilaterally increase dopamine release in much of the neostriatum. This increase in release also appears to be strongest in the posterolateral neostriatum, an area which may have a sensorimotor function.

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