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BRIEF COMMUNICATION

Different Patterns of Rotational Behavior in Rats After Dorsal or Ventral Striatal Lesions With Ibotenic Acid

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KAFETZOPOULOS, E., V. VLAHA AND S. KONITSIOTIS. *Different patterns of rotational behavior in rats after dorsal or ventral striatal lesions with ibotenic acid.* PHARMACOL BIOCHEM BEHAV **29**(2) 403–406, 1988.—Rats with total, dorsal or ventral ibotenic acid striatal lesions were challenged with DA agonists apomorphine and d-amphetamine. In rats with total lesions, both drugs induced an intense ipsilateral rotation, as did apomorphine in the dorsally lesioned rats. Amphetamine induced ipsilateral rotation in ventrally lesioned rats, but this effect may represent a non-specific potentiation of spontaneous ipsilateral rotation observed in this group. These results indicate that the neostriatum of the rat is not an homogeneous structure concerning the expression of rotational behavior after DA receptor stimulation.

Rotational behavior Corpus striatum Ibotenic acid Apomorphine d-Amphetamine

PERHAPS the most extensively used test of neostriatal dopamine (DA) function is rotational behavior following unilateral lesions of the nigrostriatal pathway in which direct acting DA receptor agonists cause contralateral rotation, presumably due to the development of receptor supersensitivity on the lesioned side [24]. During the past several years, however, it has become apparent that subregions of the neostriatum contribute unequally to several different conditioned [6, 17, 20, 27] or unconditioned behaviors [18,19] that depend on DA transmission in this structure. With respect to postural asymmetries, studies in the cat revealed a functional differentiation within the neostriatum. DA injections into different striatal regions elicited contralateral head turning in some sites and ipsilateral at other sites [3,26]. In the rat, although unilateral intrastriatal crystalline DA application induced contralateral rotation [25], injections of smaller doses of DA (up to 100 ng) into various regions of the dorsal or ventral striatum did not induce postural asymmetry or rotational activity. The injections, however, did elicit a potentiation of all contralaterally directed ongoing behaviors, and this effect was most prominent after dorsal injections [13].

In the present study we present some results indicative of regional differences in ibotenic acid lesion effects [15] within the dorsal or ventral neostriatum of the rat. Although a terminology that definitely distinguishes between ventral striatum in means of nucleus accumbens and olfactory tubercle and ventrolateral caudatoputamen would be more accurate, in the present study we prefer to keep the term ventral striatum since lesion effects are hardly attributed to the very specific anatomical structures.

METHOD

Male Wistar rats, weighing 200–250 g at the time of operation, were anaesthetized with sodium pentobarbital (40 mg/kg intraperitoneally) and placed in a David Kopf stereotaxic frame. The skull of the rats was orientated according to the Paxinos and Watson atlas [21]. For dorsal striatal lesions 5 μg of ibotenic acid (Sigma) in 1 μl of saline were injected at the following coordinates: AP 0.2 mm, L 2.5 mm and V 4.5 mm (n=16). For ventral striatal lesions 5 μg of ibotenic acid in 1 μl of saline were injected at AP 0.2 mm, L 2.3 mm and V 6.5 mm (n=13). For total striatal lesions a total amount of 20 μg of ibotenic acid divided in 4 doses of 5 μg in 0.5 μl of saline was injected in 4 different points: AP 0.6 mm, L 3.0 mm, V 4.5 and 6.5 mm; AP 2.4 mm, L 2.7 mm, V 4.5 and 6.5 mm (n=9). Anteroposterior coordinates were taken from bregma, lateral from midline and ventral from skull surface. All stereotaxic injections were made with a 5 μl Hamilton syringe over a period of 3 min and the injection cannula was left in place for 5 min following each injection in

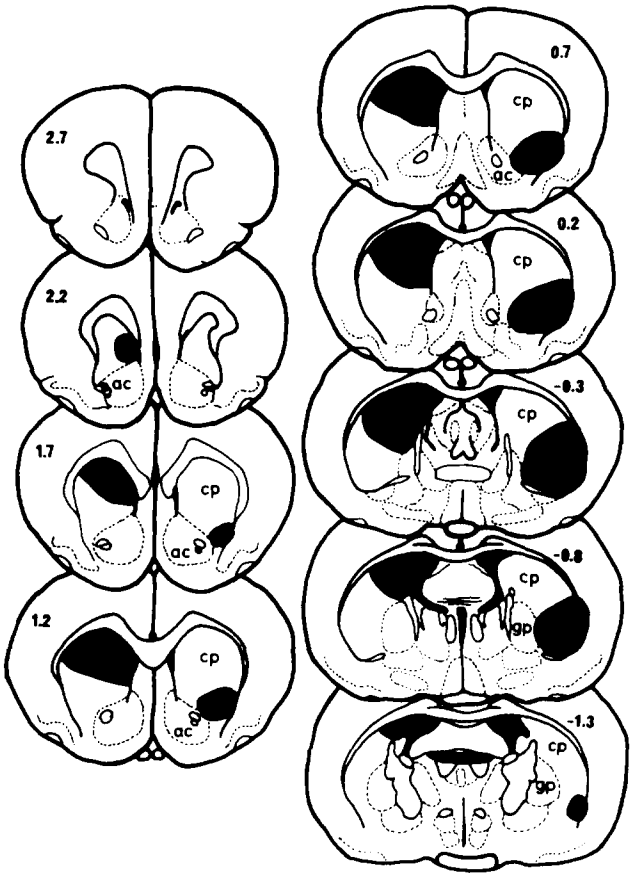

FIG. 1. Serial sections showing the localization and extent of the ibotenic acid lesions of the dorsal (left) and ventral (right) striatum in two randomly choosen rats. Dorsal and ventral lesions were transferred on the same diagrams from Paxinos and Watson atlas for easier comparison. Numbers indicate distance from bregma in mm. Abbreviations: ac—nucleus accumbens, cp—caudatoputamen, gp—globus pallidus.

order to attenuate leakage of ibotenic acid up the cannula track.

Starting one month after the operation rotational behavior was recorded using electronic rotometers connected to the I/O connector of an Apple II+ microcomputer. Prior to any drug manipulations the animals were habituated to the test apparatus for 30 min. Then they were briefly removed and injected intraperitoneally with d-amphetamine sulphate (d-AMP, Sigma) 1.5 mg/kg, apomorphine hydrochloride (APO, Sigma) 0.5 and 1.5 mg/kg, or saline. Drugs were freshly dissolved in saline containing 0.1 mg/ml ascorbic acid in the APO solution. Following the drug administration rotational behavior was recorded for 2 hours. At least three days were allowed between treatments and the order of treatment was counterbalanced.

RESULTS

After the completion of the rotation experiments histological examination of the brains in slices stained with toluidin blue, showed that intrastriatal injections of the large dose of ibotenic acid in 4 different points caused a profound loss of neuronal perikarya in the anterior and intermediate aspects of the neostriatum in all rats. The total striatal volume was

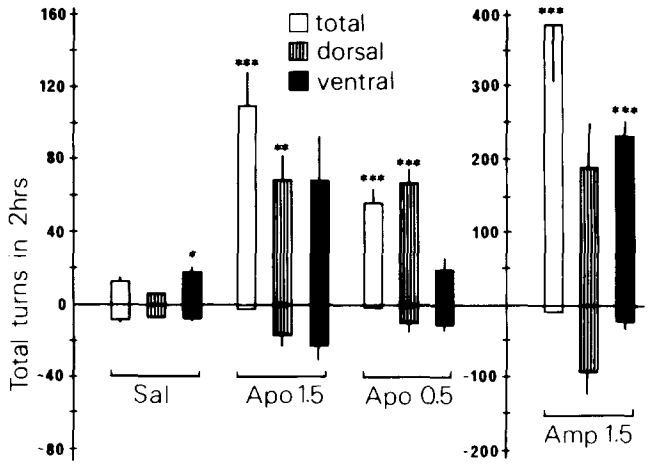

FIG. 2. Rotational behavior after saline (sal), apomorphine (Apo) 1.5 mg/kg and 0.5 mg/kg and d-amphetamine (Amp) 1.5 mg/kg in rats with total, dorsal or ventral ibotenic acid striatal lesions (mean±SEM). Positive values indicate ipsilateral rotations and negative values contralateral rotations. ***$p<0.001$, **$p<0.01$, *$p<0.05$, paired Student's t-test, ipsilateral vs. contralateral total rotations.

dramatically reduced, possibly due to the relative absence of glial proliferation within the lesioned area. Injections of the smaller dose of ibotenic acid into dorsal or ventralateral caudatoputamen induced spherically shaped lesions which were rather constant from rat to rat (Fig. 1). Microscopic examination of all the sections stained (hindbrain and midbrain) did not reveal any distant damage, except the overlying cortex and especially in the layers 5 and 6 in the total lesioned group. The only histological difference between dorsal and ventral ibotenic acid lesions was the presence of extensive gliosis within the limits of the ventral lesions, which was very restricted or absent within the limits of dorsal lesions.

The effects of systemic administration of saline, APO and d-AMP after total, dorsal or ventral striatal lesions are shown in Fig. 2. To test the hypothesis that drug-induced rotation was different after dorsal or ventral lesions, separate two-way analyses of variance (ANOVA) were performed for the APO and d-AMP scores, using the signed differences between ipsilateral and contralateral rotations as the dependent variable, and dorsal vs. ventral lesions and saline vs. drug treatment as factors. ANOVA's were followed by paired t-test comparisons between ipsilateral and contralateral rotations in all groups. The ANOVA for APO treatment revealed a significant drug effect, $F(2,83)=5.14$, $p<0.01$, and a significant lesion effect, $F(1,83)=3.25$, $p<0.05$, with a non-significant interaction, while the ANOVA for d-AMP treatment revealed a significant drug effects, $F(1,56)=12.51$, $p<0.001$, and a significant lesion effect, $F(1,56)=8.19$, $p<0.01$, without interaction. Subsequent partial paired Student's t-test comparisons showed that APO and d-AMP in rats with total lesions induced an intense ipsilateral rotation (p values are shown in Fig. 2). APO in both doses induced also an ipsilateral rotation in dorsally lesioned rats, while d-AMP induced rotation in ventrally lesioned rats. APO in ventrally lesioned rats induced rotation in both directions without any significant preference, as did d-AMP in dorsally lesioned rats. Rats with total or dorsal lesions did not show any spontaneous rotational activity, as shown from the

saline scores, but rats with ventral lesions showed an ipsilateral rotation, indicating a failure to compensate from their initial post-operative spontaneous rotation, which normally lasts for several days [7,22].

DISCUSSION

The results of the present study confirm and extend previous reports that unilateral lesions of the neostriatum in the rat induce rotational behavior after treatment with DA agonists [10,22]. The neostriatum, however, is not an homogeneous structure with respect to the behavioral outcome after dorsal or ventral lesions and this differentiation may reflect differences in efferent projections from dorsal or ventral striatum and/or regional variations in the density of striatal DA receptors.

It seems well documented that the expression of rotational behavior after DA receptor stimulation within the striatum is mediated through the striatofugal GABAergic efferents projecting to the substantia nigra pars reticulata. The rotation induced by low doses of APO or L-DOPA in unilaterally 6-OHDA denervated rats is reduced by ipsilateral knife-cuts immediately rostral to the substantia nigra [16] and the same results are produced by kainic acid lesions of the substantia nigra pars reticulata [4]. The neostriatum projects to the substantia nigra in a topographical arrangement such that the most dorsal regions project to the most ventral nigral regions (pars reticulata), while the most ventral regions project to the pars compacta and the cell group A10 and A8 [2,5]. Thus, the ipsilateral rotation observed after APO treatment in rats with unilateral dorsal lesions may reflect the unilateral activation of the striatonigral GABAergic pathway in the intact side, which results in rotational activity towards the lesioned side.

APO-induced rotation is believed to be mainly dependent on D1 receptors activation [11,12]. The observed maximal APO rotation, therefore, in dorsally lesioned rats may be due to regional variations in the density of D1 receptors in the neostriatum. DA-stimulated adenylate cyclase activity is higher in tissue taken from dorsal than from ventral striatum [1,23]. Thus, it would be expected that APO treatment in dorsally lesioned rats would activate more D1 receptors in the intact side, and elicit rotation towards the lesioned side. This finding is in agreement with two graft studies, reporting that dorsal grafts of fetal DA neurons reduced drug-induced rotation after unilateral 6-OHDA lesions to the substantia nigra, but had no effect on sensorimotor orientation or limb use [8]. By contrast, ventrolateral grafts had no effect on rotation but reduced sensorimotor bias and reinstated symmetry [9].

The opposite effects of d-AMP treatment, however, e.g., the ipsilateral rotation after ventral lesions and the lack of rotational activity after dorsal lesions, cannot be explained by this model of rotational behavior and seem to be mediated through a different mechanism. In a bilateral lesion study, we found that kainic acid lesions of the anteroventral striatum and nucleus accumbens blocked the effects of APO but not of d-AMP in locomotor activity [14]. This finding, as well as the results of the present study, indicate that APO and d-AMP differentially affect motor behaviors, and their effects could be hardly delineated solely on the basis of these results. One possible explanation, however, could be that since rats with ventral lesions exhibited a spontaneous ipsilateral rotation, d-AMP treatment resulted in a non-specific potentiation of this spontaneous rotation by enhancing the general locomotor activity of these rats, without any effect on striatal mechanisms underlying rotational behavior.

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