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Effects of Hemivibrissotomy in the Rat: Time-Dependent Asymmetries in Turning and Biogenic Amines Induced by Apomorphine

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SCHWARTING, R. K. W., H. STEINER AND J. P. HUSTON. *Effects of hemivibrissotomy in the rat: Time-dependent asymmetries in turning and biogenic amines induced by apomorphine.* PHARMACOL BIOCHEM BEHAV **35**(4) 989–994, 1990.—Behavioral and neurochemical changes accompanying unilateral removal of vibrissae were investigated in the rat. Rats were tested either 4 hours or 10 days after hemivibrissotomy. A systemic injection of apomorphine (0.5 mg/kg) induced turning behavior towards the intact vibrissae side in rats tested 4 hours after hemivibrissotomy. Compared to these animals, apomorphine induced more turning towards the side of vibrissae removal and less turning towards the intact side in animals tested 10 days after vibrissae removal. This reversal is suggestive of time-dependent changes in dopamine receptor sensitivity. Analysis of biogenic amines (dopamine, norepinephrine, serotonin) in the hemispheres ipsi- and contralateral to the side of vibrissae removal revealed evidence for neurochemical changes in apomorphine- and amphetamine-treated rats. Lateralized and bilateral differences were found in the neostriatum, septum and ventral mesencephalon, which were dependent on the side and duration of hemivibrissotomy. These results are discussed with respect to the behavioral and neural analogy between hemivibrissotomy and unilateral 6-hydroxydopamine lesions of the nigrostriatal system.

Vibrissae Turning Apomorphine Amphetamine Biogenic amines Neostriatum Mesencephalon Septum

UNILATERAL depletion of mesostriatal dopamine (DA) by intracerebral injections of 6-hydroxydopamine (6-OHDA) represents a model both for the basic understanding of this neurotransmitter system in regard to behavior and for its role in brain pathology, such as Parkinson's disease (28).

The 6-OHDA lesion of the substantia nigra, which produces a unilateral loss mainly of striatal DA, leads to asymmetrical behavioral and neuronal changes. Animals with such a lesion spontaneously turn towards the side of DA loss and show a "sensory neglect" on the side contralateral to the depletion (7, 20, 21, 35). Over time, they may recover from these sensorimotor asymmetries (21, 31, 35). There is also evidence for plasticity at the neuronal level in such rats. For one, supersensitivity of DAergic receptors develops in the denervated neostriatum, which is expressed behaviorally by a reversal in direction of turning and side of increased sensory responsiveness after systemic injections of the DA receptor agonist apomorphine (APO) (5, 14, 24, 36). Secondly, time-dependent changes occur in the crossed nigrostriatal projection, indicating that the depleted neostriatum may receive an increased input (probably DAergic) from the contralateral substantia nigra (13).

Recently, we found that a noninvasive peripheral manipulation, namely unilateral removal of the vibrissae in rats, can lead to similar behavioral and neuronal changes as the 6-OHDA lesion (15). Initially after unilateral vibrissotomy, rats preferentially scanned the walls of an open-field with the intact vibrissae side of the face; this asymmetry in thigmotactic scanning was enhanced by systemic application of APO (32). By ten days after removal of the vibrissae, rats recovered from the asymmetry in spontaneous scanning (23), and their behavioral response to APO was reversed in direction, as they now preferentially scanned with the clipped side of the face (32). This behavioral reversal is reminiscent of that seen after a unilateral 6-OHDA lesion. Furthermore, after hemivibrissotomy, rats showed a similar change in the crossed nigrostriatal projection as after the lesion: the neostriatum situated contralateral to the side lacking the vibrissae apparently receives more crossed input from the substantia nigra than the neostriatum in the ipsilateral hemisphere (12). Finally, it was shown that the occurrence of these changes in the crossed nigrostriatal projection after unilateral vibrissotomy is time-related (33) to the recovery from asymmetries in spontaneous scanning (23).

Thus, there are similarities in the effects of the 6-OHDA lesion of the substantia nigra and removal of the vibrissae, comprising changes in sensorimotor processes, in mesostriatal projections and in DAergic mechanisms. As a further investigation of this analogy, the present study was undertaken to determine a) whether unilateral vibrissotomy, like the 6-OHDA lesion, leads to turning behavior, b) if unilateral vibrissae removal results in changes in cerebral biogenic amines, and c) whether possible behavioral and/or neurochemical changes are dependent on the duration of vibrissae removal. These questions were investigated 4 hours and 10 days after hemivibrissotomy, combined with DAergic challenges such as APO and amphetamine (AMPH).

METHOD

Subjects

Fifty male Wistar rats, weighing 175–225 g at the start of the experiment, were randomly assigned to six treatment groups. They were housed in groups of five animals; each cage contained animals of different treatment groups. They received tap water and rat chow ad lib, and were kept under a normal 12-hr light:12-hr dark cycle.

Vibrissae Removal

The animals were handled and weighed daily for 10 days prior to behavioral testing. On the first day, the mystacial vibrissae, and those on the cheek and brow (11) were unilaterally clipped in three of the six groups (10-DAYS groups). Clipping with an electrical hair clipper took about 10 sec per rat. On the following days the regrown bristles of the vibrissae were removed in an identical manner. In the remaining three groups the vibrissae were left intact until 4 ± 1 hours before behavioral testing was begun (4-HOURS groups), when they were also clipped on one side of the face. The side of vibrissae removal (left or right) was counterbalanced within each group.

Behavioral Testing and Drug Administration

On day 11, all rats were tested for behavioral asymmetries 4 ± 1 hours after treatment of the vibrissae. The testing apparatus consisted of a wooden chamber ($60 \times 60 \times 40$ cm, with black walls and floor) and a video image analyzing system (VIAS), which records the analog video image on tape and analyzes the digitized (bit) image of the rat in terms of rotations and locomotion (3). Testing was carried out under red light between 14.00 and 17.00 hr. Prior to testing the rats received injections (SC, in the neck) in a separate room. Two groups received injections of saline (groups 4-HOURS + SALINE and 10-DAYS + SALINE; n = 8 each), two groups amphetamine (1 mg/kg; groups 4-HOURS + AMPH and 10-DAYS + AMPH; n = 8 each), and two groups APO (0.5 mg/kg; groups 4-HOURS + APO and 10-DAYS + APO; n = 9 each). Between drug administration and testing each animal was kept singly in a separate room for 10 minutes. Behavioral recording was begun about 11 minutes after drug injection. The rat was placed into one corner of the testing apparatus with its head pointing to the center of the chamber. The behavioral parameters recorded over a period of 5 minutes by VIAS were: a) the distance traversed by the rat as a measure of locomotor activity, and b) turning behavior (the number of quarter turns with a diameter of less than 30 cm).

Drugs

All drugs were prepared on the day of testing. AMPH (amphetamine sulfate; Knoll AG; calculated as the salt) was dissolved in saline to a concentration of 0.5 mg/ml; APO (Woelm Pharma) was dissolved to a concentration of 0.25 mg/ml. Saline-injected animals received a volume of 2 ml/kg.

Neurochemical Analysis

Immediately after behavioral testing the animals were sacrificed under light ether anesthesia. After decapitation, the following brain samples were dissected out on ice-cold glass plates: 1) neostriatum (using the globus pallidus and the anterior commissure, where it crosses the midline, as the caudal border); 2) septum (ventrally bordered by the edges of the lateral ventricles and caudally by the level of the anterior commissure, where it crosses the midline); and 3) ventral mesencephalon, including substantia nigra and ventral tegmental area (dorsally bordered by the level of the ventral part of the lateral geniculate body).

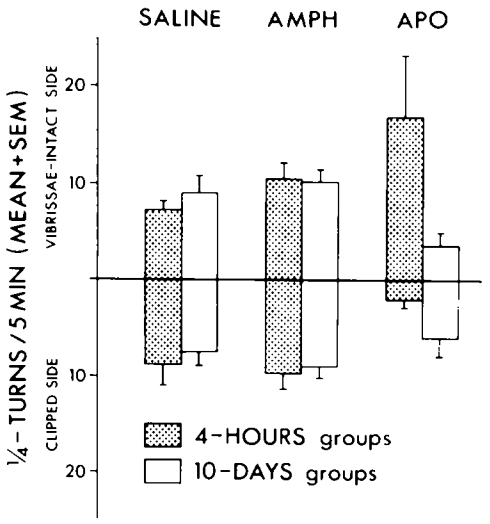

FIG. 1. Turning behavior towards the vibrissae-intact side versus the side of unilateral vibrissae removal (clipped side). Turning behavior during a testing period of 5 minutes is expressed as quarter turns with a diameter of less than 30 cm (mean + SEM). Rats were tested either 4 hours (4-HOURS groups, stippled bars) or 10 days after hemivibrissotomy (10-DAYS groups, open bars). Prior to behavioral testing they received a subcutaneous injection of either the vehicle solution (SALINE, n = 8 each), 1.0 mg/kg amphetamine (AMPH, n = 8 each), or 0.5 mg/kg apomorphine (APO, n = 9 each).

Each sample was analyzed by means of high-performance liquid chromatography with electrochemical detection [using methods described elsewhere (29)]. The following substances were measured: dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 3-methoxytyramine (3-MT), norepinephrine (NE), serotonin (5-HT), and 5-hydroxyindole-3-acetic acid (5-HIAA).

Statistics

Behavioral and neurochemical data were expressed as means and standard errors of the mean. Behavioral data were analyzed by means of Student's *t*-test, using the paired *t*-test for dependent samples for within-group comparisons and the *t*-test for independent samples for between-group comparisons. Neurochemical data were analyzed between animals of the same pharmacological treatment by means of two-way ANOVA for repeated measures (factor A: duration of vibrissae removal; factor B: side of brain area in relation to vibrissae removal) followed by *t*-tests.

RESULTS

Behavioral Measures

Neither saline- nor amphetamine-treated animals showed asymmetries in quarter turns (diameter less than 30 cm) with respect to the side of vibrissae removal (paired *t*-tests, one-tailed, $p > 0.050$; Fig. 1). In contrast, asymmetries were found in APO-injected animals. When tested 4 hours after vibrissae removal, such rats showed more quarter turns ('head-to-tail') to the intact vibrissae side than to the clipped side (4-HOURS + APO: $p = 0.029$). On the other hand, APO-injected animals, tested 10 days after vibrissae

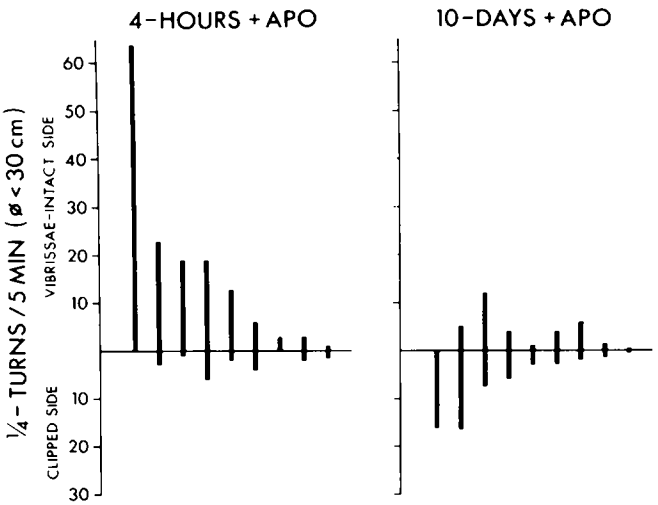

FIG. 2. Individual turning data (quarter turns in 5 minutes) from rats tested with apomorphine (0.5 mg/kg SC) either 4 hours (4-HOURS+APO, left half) or 10 days after hemivibrissotomy (10-DAYS+APO, right half). Turning behavior is expressed as towards the vibrissae-intact side versus the side of unilateral vibrissae removal (clipped side).

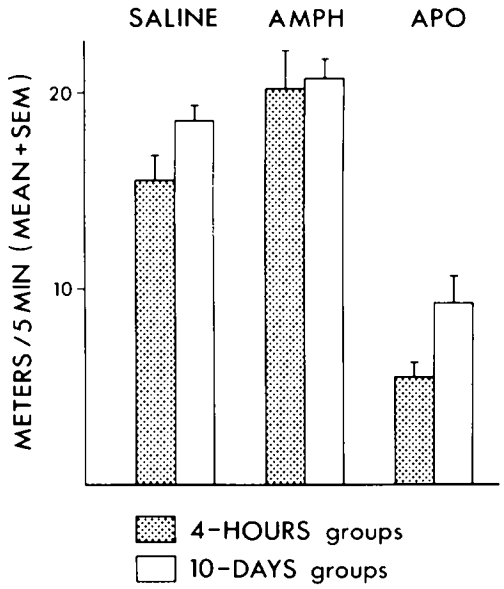

FIG. 3. Locomotor activity expressed as meters in 5 minutes (mean+SEM) in rats tested either 4 hours (4-HOURS groups, stippled bars) or 10 days after hemivibrissotomy (10-DAYS groups, open bars). Prior to behavioral testing they received a subcutaneous injection of either a vehicle solution (SALINE, n=8 each), 1.0 mg/kg amphetamine (AMPH, n=8 each), or 0.5 mg/kg apomorphine (APO, n=9 each).

removal, showed a different behavioral pattern, as turning behavior to the clipped and vibrissae-intact side was balanced (10-DAYS + APO: $p = 0.169$). However, compared to the 4-HOURS + APO group they showed a higher rate of turning to the side of vibrissae removal ($p = 0.043$) and a lower rate of turning to the intact side ($p = 0.033$). Therefore, a reversal in the direction of APO-induced behavioral asymmetry was observed 10 days after vibrissae removal. Furthermore, when looking at individual turning data of these two animal groups (Fig. 2), it becomes apparent, for one, that under both conditions of vibrissae removal those animals which showed the most turning behavior after APO were the most asymmetrical, and secondly, that such animals turned to the intact side when tested 4 hours after removal of the vibrissae, but turned to the clipped side when tested 10 days after hemivibrissotomy.

Further differences between groups were found in the measure of locomotor activity (Fig. 3). Locomotor activity after APO was higher in animals tested 10 days than in those tested 4 hours after vibrissae removal (*t*-test for independent samples; 4-HOURS + APO versus 10-DAYS + APO: $p = 0.024$). In saline- and AMPH-treated animals no substantial difference in locomotor activity with respect to the duration of vibrissae removal was observed (4-HOURS + SALINE versus 10-DAYS + SALINE: $p = 0.096$; 4-HOURS + AMPH versus 10-DAYS + AMPH: $p = 0.413$).

Neurochemical Analysis

The analysis of variance gave no indications for significant differences in saline-treated animals, neither with respect to duration or side of vibrissae removal, nor with respect to an interaction between the two factors. In AMPH-treated animals, tested 4 hours after vibrissae removal (4-HOURS + AMPH), the level of neostriatal 3-MT was higher ipsilateral to the side of vibrissae removal than contralateral ($p = 0.034$; see Table 1).

In APO-treated animals, differences were observed in all 3 brain areas. In the neostriatum of the 4-HOURS group, the level of 5-HT was higher contralateral to the side of vibrissae removal than ipsilateral ($p = 0.020$). In the septal nucleus of the clipped side, the level of 5-HT was higher 4 hours than 10 days after vibrissae removal ($p = 0.042$). Finally, in the ventral mesencephalon, bilateral differences were observed: the levels of DOPAC ($p = 0.019$), HVA ($p = 0.016$), and NE ($p = 0.004$) were lower 4 hours than 10 days after vibrissae removal.

DISCUSSION

The present results show for one, that unilateral vibrissae removal can lead to asymmetries in APO-induced turning behavior. In the acute state, that is, 4 hours after vibrissae removal, rats turned towards the side of intact vibrissae when challenged with the DA receptor agonist APO. Szechtman (34) observed similar turning behavior towards the sensory intact side under APO after bandaging one side of the rats' face (including nostrils, snout, vibrissae, chin, eye and ear), thus influencing multiple sensory systems. The present data show that an imbalance in vibrissae input alone is sufficient to induce turning behavior under APO. Similar effects of hemivibrissotomy on turning behavior were found in a subsequent study (22). Thus, unilateral vibrissae removal does not only lead to asymmetries in thigmotactic scanning (32), but also in drug-induced turning behavior. The direction of these behavioral asymmetries seems to depend on sensory input from the intact vibrissae side, as both behavioral asymmetries are directed towards this side. However, it is important to note that the required motor response is opposed in the two cases: for example, an animal shaved on the left side of the face moves clockwise; i.e., towards the intact side, when turning (present results), but moves counter-clockwise when scanning along the walls of the open-field with the intact side (32). Thus, it is unlikely that these behavioral asymmetries are due to asymmetries in motor function.

In the previous study, we observed a reversal of behavioral asymmetry after 10 days of hemivibrissotomy, since animals tested under APO 10 days after vibrissae removal scanned signif-

TABLE 1

HEMIVIBRISSOTOMY AND BIOGENIC AMINES

	Neostriatum							Septum				Mesencephalon					
	DA	DOPAC	HVA	3-MT	NE	5-HT	5-HIAA	DA	DOPAC	NE	5-HT	DA	DOPAC	HVA	NE	5-HT	5-HIAA
4-HOURS + SALINE																	
clipped side	8.36	1.42	0.73	0.42	0.08	0.21	0.34	0.75	0.10	0.55	0.54	0.79	0.20	0.17	0.61	1.03	0.98
	±0.49	±0.08	±0.09	±0.05	±0.02	±0.01	±0.02	±0.11	±0.02	±0.06	±0.06	±0.05	±0.02	±0.01	±0.02	±0.08	±0.08
intact side	8.25	1.37	0.73	0.43	0.08	0.21	0.35	0.74	0.13	0.49	0.45	0.78	0.20	0.16	0.59	0.92	0.92
	±0.40	±0.08	±0.08	±0.05	±0.01	±0.01	±0.03	±0.07	±0.03	±0.08	±0.09	±0.07	±0.02	±0.01	±0.02	±0.05	±0.05
10-DAYS + SALINE																	
clipped side	8.21	1.25	0.55	0.30	0.05	0.20	0.29	0.79	0.10	0.32	0.29	0.64	0.17	0.15	0.58	0.97	0.97
	±0.36	±0.03	±0.07	±0.03	±0.01	±0.01	±0.01	±0.10	±0.02	±0.07	±0.12	±0.04	±0.01	±0.02	±0.02	±0.04	±0.05
intact side	8.25	1.28	0.56	0.31	0.05	0.21	0.34	0.75	0.10	0.40	0.45	0.72	0.18	0.16	0.58	0.95	0.96
	±0.39	±0.08	±0.09	±0.04	±0.01	±0.02	±0.01	±0.12	±0.02	±0.13	±0.17	±0.05	±0.02	±0.02	±0.02	±0.04	±0.04
4-HOURS + AMPH																	
clipped side	9.15	0.89	0.59	0.49	0.08	0.22	0.32	0.68	0.05	0.37	0.39	0.64	0.15	0.14	0.62	1.07	0.96
	±0.14	±0.03	±0.07	±0.06 *	±0.02	±0.02	±0.03	±0.07	±0.02	±0.04	±0.08	±0.04	±0.01	±0.01	±0.01	±0.07	±0.06
intact side	8.59	0.83	0.55	0.41	0.09	0.23	0.31	0.70	0.06	0.43	0.28	0.70	0.17	0.16	0.62	1.12	0.98
	±0.35	±0.03	±0.07	±0.06	±0.02	±0.02	±0.03	±0.09	±0.03	±0.07	±0.09	±0.05	±0.01	±0.02	±0.03	±0.08	±0.06
10-DAYS + AMPH																	
clipped side	8.62	0.89	0.56	0.36	0.08	0.22	0.32	0.94	0.10	0.52	0.48	0.75	0.17	0.16	0.59	1.11	0.95
	±0.64	±0.07	±0.07	±0.04	±0.01	±0.01	±0.01	±0.14	±0.03	±0.11	±0.11	±0.06	±0.01	±0.01	±0.01	±0.07	±0.05
intact side	9.37	0.97	0.60	0.38	0.08	0.21	0.32	0.98	0.09	0.50	0.44	0.73	0.16	0.16	0.59	1.03	0.93
	±0.54	±0.04	±0.08	±0.04	±0.01	±0.01	±0.01	±0.16	±0.03	±0.12	±0.10	±0.04	±0.01	±0.01	±0.02	±0.06	±0.05
4-HOURS + APO																	
clipped side	9.16	0.74	0.35	0.20	0.04	0.20	0.32	0.87	0.06	0.34	0.50	0.76	0.11	0.12	0.53	0.97	0.97
	±0.44	±0.03	±0.04	±0.03	±0.01	±0.01 *	±0.03	±0.13	±0.02	±0.07	±0.09	±0.07	±0.01	±0.01	±0.02	±0.06	±0.09
intact side	9.37	0.74	0.35	0.20	0.03	0.24	0.33	0.86	0.01	0.27	0.39	0.73	0.13	0.12	0.56	1.00	1.02
	±0.29	±0.04	±0.05	±0.02	±0.00	±0.02	±0.03	±0.10	±0.01	±0.07	±0.08 *	±0.03	±0.01	±0.01	±0.01	±0.06	±0.11
10-DAYS + APO														*	*	†	
clipped side	9.86	0.77	0.45	0.23	0.05	0.21	0.29	0.56	0.04	0.34	0.26	0.76	0.14	0.14	0.60	1.02	1.02
	±0.41	±0.03	±0.05	±0.03	±0.01	±0.01	±0.02	±0.09	±0.02	±0.06	±0.06	±0.04	±0.01	±0.01	±0.01	±0.04	±0.04
intact side	10.14	0.80	0.46	0.24	0.05	0.21	0.30	0.61	0.04	0.32	0.38	0.76	0.15	0.15	0.60	0.98	1.00
	±0.40	±0.05	±0.07	±0.04	±0.01	±0.01	±0.02	±0.09	±0.01	±0.05	±0.06	±0.03	±0.01	±0.01	±0.01	±0.04	±0.04

Levels (in μg/g brain tissue; means ± SEM) of DA and its metabolites DOPAC, HVA and 3-MT, NE, and 5-HT and its metabolite 5-HIAA in brain samples from rats analyzed 4 hours or 10 days after hemivibrissotomy. Prior to behavioral testing and subsequent neurochemical analysis rats received a subcutaneous injection of either vehicle (SALINE), 1.0 mg/kg amphetamine (AMPH), or 0.5 mg/kg apomorphine (APO). Results are expressed as either ipsilateral (clipped side) or contralateral (intact side) to the side of vibrissae removal. Differences within or between groups according to two-way ANOVA for repeated measures and *t*-tests: *$p<0.05$, †$p<0.01$.

icantly more with the clipped side than with the intact vibrissae side (32). In analogy to the APO-induced reversal in direction of turning seen after a unilateral 6-OHDA lesion of the substantia nigra (36), we suggested that the observed behavioral reversal could be due to the development of DA receptor supersensitivity in the neostriatum contralateral to the side of vibrissae removal (i.e., the vibrissae-deprived hemisphere). In the present study, animals tested under APO 10 days after vibrissae removal showed a higher rate of turning ipsiversive to the side of vibrissae removal and a lower rate of contraversive turning than the animals tested 4 hours after vibrissae removal. The data from individual animals (10-DAYS + APO group, Fig. 2) show that those rats which exhibited the most turning behavior turned predominantly towards the clipped side. Thus, the present results are also indicative of a behavioral reversal after 10 days of hemivibrissotomy. This reversal might be due to the development of supersensitive DA receptors in the hemisphere contralateral to the side of vibrissae removal, which, when challenged with the receptor agonist APO, not only leads to a reduction of turning to the vibrissae side, but can even lead to turning behavior towards the clipped side.

The absence of behavioral asymmetry in saline- and AMPH-treated rats may be a result of the measure used, since other studies have shown asymmetries in scanning behavior in undrugged or AMPH-treated hemivibrissotomized rats (22, 23, 32). Similarly, after unilateral 6-OHDA lesions of the substantia nigra, the measures of turning and scanning can differ in their sensitivity to reveal sensorimotor asymmetries (31).

The present study also provides evidence for neurochemical changes after hemivibrissotomy in the form of lateralized and bilateral differences within and between groups. After AMPH, there was an asymmetry in neostriatal 3-MT levels in animals tested 4 hours, but not 10 days after hemivibrissotomy, with a higher level ipsilateral to the side of vibrissae removal. AMPH is known to increase 3-MT levels in neostriatal homogenates (6, 37,

38), and neostriatal 3-MT levels may reflect the release of DA [(16, 26, 38, 39); for review see (40)]. Therefore, the asymmetry in striatal 3-MT levels after AMPH supports the hypothesis that unilateral vibrissae removal can lead to time-dependent asymmetries in dopaminergic mechanisms in the neostriatum (15).

After APO, we observed an asymmetry of neostriatal 5-HT in the 4 hours group and a lateralized difference in septal 5-HT between the 4 hours and 10 days groups. APO influences 5-HT either by a direct action on the dorsal raphe system (18) or by mediation through dopaminergic neurons (19). The present results, therefore, provide new evidence for an asymmetrical role of biogenic amines in the septum, which was also indicated in another experiment in which asymmetrical handedness was analyzed (30). Interestingly, several studies have implicated the septum in vibrissae function (10,17) and in tactile reactivity (4,9).

In the ventral mesencephalon we observed bilateral differences of DOPAC, HVA and NE between 4-HOURS + APO and 10-DAYS + APO, with the lower levels always apparent 4 hours after vibrissae removal. These bilateral differences might be related to the differences found in locomotor activity, since catecholamines in the ventral mesencephalon (ventral tegmental area, substantia nigra) play a role in locomotor activity [e.g., (2,8)]. Thus, a functional relationship seems likely between the chemical and behavioral effects observed here.

In the present study we did not observe dopaminergic asymmetries in the neostriatum in the 4-HOURS + APO group. This is in contrast to results from another study (15), in which we found lateralized striatal changes under APO 4 hours after vibrissae removal. In that study, animals received sham treatment during 10 days before actual vibrissae removal, and, thus, were habituated to this treatment, whereas in the present study they were not. Furthermore, unlike in the present study, the animals had also been habituated to the testing environment. Thus, in the present study, it cannot be ruled out that factors such as stress [for review see (1)] or sensory stimulation (25,27) during clipping of the vibrissae contributed to the neurochemical results. It remains to be determined whether the lateralized stimulation during clipping of the vibrissae can affect biogenic amines as long as 4 hours after this treatment.

In summary, the present results provide further evidence for time-dependent behavioral and neural changes after hemivibrissotomy. Previous results suggested an interesting analogy between hemivibrissotomy and the unilateral 6-OHDA model [for review see (15)]. Hemivibrissotomy, like the unilateral 6-OHDA lesion, leads to time-dependent changes in the crossed nigrostriatal projection (12,33), to asymmetries in scanning behavior (32), to time-dependent behavioral recovery (23), and to changes in the direction of APO-induced thigmotactic scanning (32), which might be related to DA receptor supersensitivity (5,36). The data of the present experiment show that after hemivibrissotomy, as after the 6-OHDA lesion, APO can induce asymmetries in turning behavior, the direction of which is dependent on the duration of vibrissae removal. Furthermore, the results indicate that these behavioral changes are paralleled by changes of biogenic amines in the brain. Thus, unilateral vibrissae removal might serve as an additional model to the 6-OHDA lesion, as it provides the major advantage [for detailed discussion see (15)] that no surgical brain intervention is required.

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