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A10 Lesion and Passive Avoidance Latency: Correlation with Limbic Tyrosine-Hydroxylase-Activity

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RAAB, A. AND G. KOJER. *A10 lesion and passive avoidance latency: Correlation with limbic tyrosine-hydroxylase-activity*. PHARMAC. BIOCHEM. BEHAV. 17(1) 77–83, 1982.—Experiments were carried out with female tree-shrews (*Tupaia belangeri*). Following 6-hydroxydopamine injections into the ventral tegmental area, considerable variations in tyrosine-hydroxylase activity in the respective target regions of the A10 area occurred. Depletion of the THY-activity in the septum (SE), the entorhinal cortex (ECO), the frontal cortex and the basal ganglia correlated with an impairment in the performance of a passive avoidance task (indicated by testing 24 hours postshock). Partial correlation analysis revealed that the variations of THY-activity in the SE and ECO are primarily related to this failure in passive avoidance acquisition.

A10 lesion 6-Hydroxydopamine Tyrosine-hydroxylase Septum Entorhinal cortex Passive avoidance

THE ventral tegmental area (VTA) has been the subject of many investigations. Lesions in this area cause a behavioral syndrome including hyperactivity and hyperreactivity, footspreading, disappearance of the freezing reaction and failure in passive avoidance tasks [11,17].

The dopaminergic cells of the ventral tegmental area, the A10 dopaminergic group, innervate cortical, limbic and other parts of the basal forebrain [2, 7, 8, 9, 18, 32]. Le Moal and coworkers demonstrated that the hyperactivity which occurs after destruction of A10 region is correlated with a decrease of dopamine (DA) levels in the frontal cortex, one of the target regions of the A10 neurons. The performance of a passive avoidance task of these animals is also impaired [11,17]. However, no individual correlations between this behavior and the dopamine metabolism in the respective target regions of A10 have been published until now.

We have recently shown that subordinate tree-shrews confronted with social conflict show an increase of the activity of tyrosine-hydroxylase (THY) in the septal area if they cope successfully with the conflicting social situations. These animals acquire a passive avoidance behavior. In contrast with these, subordinates which cannot cope successfully with social conflict, show a decrease of THY-activity in this brain area [27]. The DA turnover correlates with the activity of this enzyme, which is rate-limiting for the synthesis of DA [3]. The septal area is one of the target regions of the dopaminergic neurons in the VTA. In addition, these facts suggest a role of the mesolimbic dopaminergic system in this behavior. To tackle the problem to what degree the septum and the other target regions of A10 contribute to this behavior, we decided to undertake a partial correlation analysis.

To exclude other effects of social conflict on brain and behavior such a study has to be carried out in animals that are kept isolated. Among singly housed tree-shrews, however, there is practically no variation of THY-activity in the septum and in other target regions of A10 [27,28]. Under such circumstances the conditions for a correlation analysis are not given.

To induce such variations in the target areas of A10 we, therefore, injected 6-hydroxydopamine (6-OHDA) into the VTA, which leads to loss of catecholaminergic neurons. It is the aim of this drug treatment to make this correlation analysis possible and not to demonstrate whether chemically lesioned animals perform better or worse in a passive avoidance task. To include animals without 6-OHDA treatment into the study, therefore, would not provide additional information. In the principal target regions, as well as in other parts of the brain, THY-activity was measured as an indicator of surviving DA-synapses. Individual correlations and a correlation analysis between the THY-activity in these brain areas and passive avoidance latency are presented.

METHOD

Subjects

Eight adult female tree-shrews *(Tupaia belangeri)* weighing between 160 g and 220 g were used. The animals were kept isolated under an artificial day:night change of 12:12

hours and a temperature of about 23°C. Food (Altromin diet for *Tupaia*) and water were always freely available.

Stereotaxic Coordinates

Medial VTA lesions were produced, with reference to a brain atlas [34], at coordinates AP 0.5; L 0.45; DV 1.1 from interaural zero. Because of bloodvessels in the midline we passed through an overlying tissue at an angle of 20 degrees to the vertical. The coordinates were adjusted with a David Kopf Stereo-taxic Apparatus adapted to tree-shrews. Differences in coordinates were based on our animals being larger than those used in preparation for the brain atlas.

Injections

The animals were operated under Nembutal anesthesia (0.18 mg/100 g IM). The lesions in the A10 were made by using 6-hydroxydopamine (6-OHDA-hydrochloride, EGA-Chemie, 7924 Steinheim, West Germany) which destroys catecholaminergic neurons. Volumes of 1.0 μl at the concentration of 2 μg/μl were injected through a glass micropipette which remained in place for 5 minutes following the injection.

General Processing

The animals were killed between 8:00 and 8:30 a.m. by incision of the left carotid. The brains were dissected within three minutes after the carotid incision. The mesencephalon was cut out and kept in a Formalin solution (10%); the remaining tissues were frozen at −35°C. THY was assayed within three days after death. Before assay the brains were dissected into the following parts: frontal cortex (FCO), cortex (CO), septum (SE), hippocampus (HIP), entorhinal cortex including the amygdala (without the N. tractus olfactorii and the anterior part of the N. medialis amygdalae) (ECO), basal ganglia (BAS), hypothalamus (HTH) and nucleus accumbens (ACC).

The assay of the THY was carried out as described previously [24,28]. The midbrain was kept in the formalin solution for four to eight weeks. Eighty μm coronal sections were made using a cryostat and were impregnated using the Fink-Heimer method [10].

Behavioral Studies

Our testing box consisted of a 50×50×30 cm box and a 50 cm long alley with a grid floor. At the end of the alley mealworms were given as a reward. The animal's sleeping box could be connected to an opening in the testing apparatus facing the alley; this opening was covered with a removable guillotine door. After having connected the sleeping box containing the animals to the testing apparatus the guillotine door remained closed for 10 minutes in order to minimize effects of handling. After having opened the door the following three parameters were recorded in minutes: (a) latency to leave the sleeping box (leave); (b) latency to enter the alley (enter); (c) latency to start eating mealworms (eat).

In the first experiment the tree-shrews were trained in one training session per day to eat mealworms until their eat-latencies were constant and less than three minutes. Twenty to thirty training sessions were necessary to reach this criterion. Animals achieving this criterion performance early, continued to be tested every 2 to 3 days until all animals of a group had learned the task. All animals received lesions on the following day. For wild animals such as tree-shrews such training periods are not unusual. In contrary to them, white rats which have been adapted to laboratory conditions for many generations, are less shy and become more easily acquainted to a testing apparatus.

Following the lesion the animals were given a period of six to seven days to recover. Upon reintroduction to the task all animals performed at pre-known levels—that is, the lesion itself resulted in no performance decrement. Training was continued until the 20–25th postoperative day. During the last training session, while eating, each animal received for 5 seconds a 1.8 mA scrambled electric foot shock. Twenty-four hours later the above mentioned parameters ("leave," "enter," "eat") were tested. Afterwards the animals were retrained to the criterion of eat-latency (6 days) and the same testing procedure was repeated.

TABLE 1

MEANS, STANDARD DEVIATIONS AND STANDARD DEVIATIONS AS PERCENTAGE OF THE MEAN OF THY-ACTIVITY (nmol/g/hr) IN ALL BRAIN AREAS MEASURED

Brainpart	Mean (nmol/g/hr)	Standard Deviation	% Standard Deviation
SE	80.6	54.3	67.3
ECO	11.5	4.5	39.6
FCO	9.4	2.8	33.5
HIP	3.2	1.1	34.0
CO	5.5	1.4	26.0
ACC	83.4	19.4	23.3
BAS	122.6	24.8	20.2
HTH	37.7	8.4	22.1

Data Analysis

All data obtained from the present study were statistically evaluated by SPSS (Statisical Package for the Social Sciences) for partial correlations of zero order, of first and second order (Pearson correlation coefficient) and for parallel t-test [25].

RESULTS

Biochemistry

Thirty days approximately after VTA lesion large variations of the THY levels occurred in the principal target areas of A10 dopaminergic neurons. Other brain regions ahowed only minor variations. Table 1 shows the standard deviation as a percentage of the mean for every brain area measured. SE and ECO show the most prominent standard deviation. The HTH, which is not innervated by the A10, but is adjacent to the injection site and could even be affected by diffusing 6-OHDA, shows only minor variation. The BAS shows also minor standard deviation, though it is innervated by the substantia nigra (A9) which is adjacent to the injection site. In the case of HIP and CO the relatively low content of THY itself presumably induces greater errors in measurement (Table 2). There are good correlations among the variations of THY-activity in the principal target regions of the A10: SE, ECO, FCO, ACC and BAS. Significant correlation among the THY-activity in target regions and other parts of

TABLE 2

CORRELATION COEFFICIENTS AMONG THE VARIATION OF THY-ACTIVITY IN THE PRINCIPAL TARGET REGIONS OF A10 AND OTHER BRAIN AREAS

	Zero Order Correlation Coefficient							
	SE	ECO	FCO	ACC	BAS	CO	HTH	HIP
SE		0.91 0.0001	0.73 0.02	0.74 0.02	0.63 0.04	0.54 0.09	−0.01 0.70	−0.04 0.50
ECO			0.73 0.02	0.78 0.02	0.82 0.01	0.59 0.06	0.18 0.30	0.19 0.30
FCO				0.79 0.02	0.65 0.04	0.60 0.06	0.41 0.10	0.06 0.40
ACC					0.40 0.10	0.58 0.06	0.37 0.30	0.23 0.30
BAS						0.54 0.09	0.56 0.07	0.47 0.10
CO							0.28 0.20	0.09 0.30
HTH								0.53 0.09

Target and non-target regions are separated by a vertical line. The upper figures indicate the r-values, the lower ones the corresponding p-values.

the brain (HIP, CO, HTH) were not detected. Table 2 shows the correlation coefficients among the variations of the THY-activity in the principal target regions of A10 and other areas of the brain.

Behavior

Table 3 shows the mean values for the three defined avoidance latencies and standard deviations in the first and second postshock trials. For the group, shock treatment during the last training session resulted in a significant lengthening of all parameters measured. However, as can be seen in Fig. 1, profound individual variation in passive avoidance behavior was observed. It is apparent from this figure that the difference in eat-latency following shock varied between animals from $3^1/_2$ to 32 minutes. Thus, some animals showed excellent passive avoidance, while others showed virtually none. This situation allowed us to undertake individual correlations between THY-activity after A10 lesions and behavioral performance.

Correlation of Neurochemical and Behavioral Data

Significant correlation between neurochemical and behavioral data was found only within the "eat" parameter. Parameters "leave" and "enter" did not correlate with THY-activity in any of the brain areas examined. The individual correlations of eat-latency and THY levels in areas examined are shown in Table 4. Failure in the passive avoidance task was correlated with low THY-activity in SE and ECO. BAS and FCO also showed significant correlations. THY-activity in the HTH, HIP, CO and ACC did not correlate significantly with passive avoidance failure. In Fig. 2 the regression between latency and THY-activity of SE and ECO is shown.

As we have described above, comparable alterations in THY-activity in the respective targets of A10 were observed following destruction of this region. However, the ACC, one of these target regions, showed no significant correlation with the passive avoidance deficit. This raises the question whether the respective target areas of the A10 region are all to the same degree involved in inducing this deficit. To tackle this problem we undertook a partial correlation analysis, allowing us to examine the degree of influence of each of the respective brain areas on behavior (Table 5).

The second order Pearson correlation coefficient controlling for the effects of SE and ECO leads to a complete disappearance of any correlation between the passive avoidance deficit and the THY content of BAS and FCO. On the other hand, a significant Pearson correlation coefficient between the behavior and THY-activity in SE and ECO was maintained by controlling for the effects of BAS and FCO at second order partial correlation (Table 5). The first order Pearson correlation coefficient controlling for BAS and FCO confirms these results. The Pearson correlation coefficient of the first order controlling for either the effect of ECO on SE or vice versa, indicates a comparable but not significant effect of these brain areas on passive avoidance.

Histological Results

The system of DA-cell bodies in VTA and in pars compacta of the substantia nigra of the tree-shrew has a distribution similar to the corresponding DA-cell system in the rat [6]. On the Fink-Heimer impregnated sections cell degeneration in the VTA occurs to different degrees (Fig. 3a,b,c). Such cell loss could not be detected in other nuclei of the coronal sections of the midbrain. However, it was not possible for us to coordinate with certainty the amount of degeneration observed with the neurochemical changes in the target regions. Thirty to thirty-five days following the

TABLE 3

MEDIAN LATENCIES (min) AND STANDARD DEVIATIONS OF THE PRE-SHOCK AND POST-SHOCK LATENCIES FOR THE PARAMETERS "LEAVE," "EAT," "ENTER" (FIRST AND SECOND TRIAL)

	Mean-Latency (min)					
	First Trial			Second Trial		
	pre-shock	post-shock	p	pre-shock	post-shock	p
"Leave"	2.12 ± 0.33	7.0 ± 2.2	0.05	2.21 ± 0.34	7.8 ± 2.3	0.02
"Enter"	2.15 ± 0.33	11.0 ± 2.4	0.009	2.26 ± 0.34	12.4 ± 2.3	0.002
"Eat"	2.18 ± 0.33	14.5 ± 3.2	0.006	2.30 ± 0.34	17.0 ± 2.8	0.001

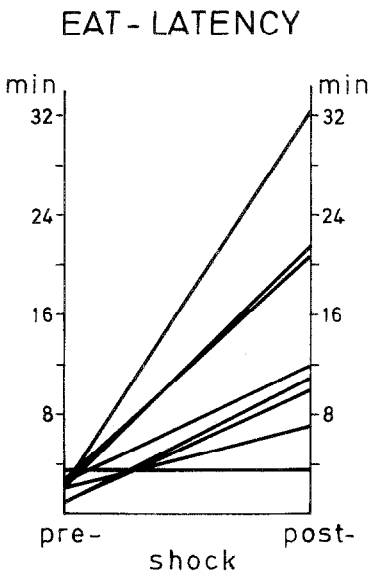

FIG. 1. Individual differences of the "eat"-latencies (min). Both, pre-shock and post-shock latencies, after the injection of 6-OHDA into the VTA.

injection no traces of the tracks of the injection cannulae (diameter of the shaft 75 μm) could be detected.

DISCUSSION

The 6-OHDA injections induce a more or less complete destruction of dopaminergic neurons in the A10 area [11]. Our injections in the VTA induced comparable variations of the THY-activity among the respective target regions of A10. Other brain regions are not affected in the same way. In our opinion the variations of the THY-activity in these target regions are due to the considerable individual variations of size and weight among the animals, which evidently result in a more or less complete destruction of the DA-neurons at the injection site; female tree-shrews housed in isolation do not spontaneously show such variations of the THY-activity in the target regions of A10 [28]. The induction of measurable variations of THY-activity in the target regions does allow for individual correlation analysis between the neurochemical and behavioral data.

The main results of our study can be summarized as follows: 6-OHDA injections into the VTA induce variation in the THY-activity of the target regions of A10; this is presumably due to different degrees of reduction of the THY-activity following the DA-cell loss in the A10 area. Low THY-activity correlates with short latencies while high THY-activity is related to long latencies in a passive avoidance task. In spite of the fact that all target regions of A10 are comparably depleted of THY-activity, only two of them are significantly involved in the impairment of passive avoidance behavior.

The theoretical argument that among 24 possible correlations (3 behavioral items and 8 neurochemical parameters) statistical significance may occur by chance only does not concern our data. A correlation of the behavioral and neurochemical data by chance is highly unlikely as the neurochemical data among the target regions of A10 are linked and not independent of each other. Therefore, the correlation of one

TABLE 4

INDIVIDUAL ZERO ORDER CORRELATIONS BETWEEN "EAT"-LATENCIES AND THE THY-ACTIVITIES IN ALL BRAIN PARTS (FIRST AND SECOND TRIAL)

	Zero-Order-Correlation-Coefficient			
	Eat-Latency		Eat-Latency	
Brainpart	1. Trial	p	2. Trial	p
ECO	0.93	0.001	0.85	0.004
SE	0.91	0.001	0.78	0.02
BAS	0.68	0.03	0.71	0.03
FCO	0.65	0.04	0.71	0.03
ACC	0.63	—	0.39	—
CO	0.62	—	0.56	—
HIP	0.14	—	0.20	—
HTH	0.04	—	0.05	—

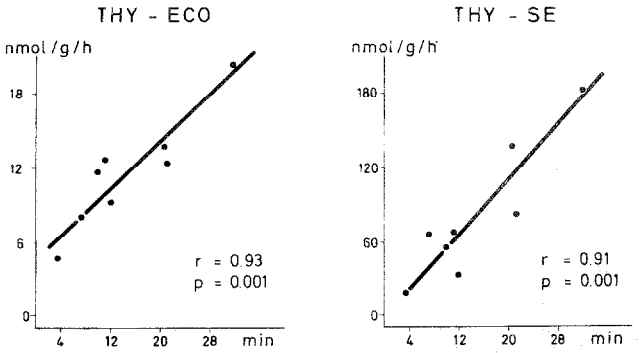

FIG. 2. Regression between the THY-activity (nmol/g/hr) of the ECO and SE and the "eat"-latency (min). "Eat"-latencies at first post-shock trial. r and p-values are indicated.

TABLE 5

FIRST AND SECOND ORDER PEARSON CORRELATION COEFFICIENTS ACCORDING TO SPSS

		ECO	SE	BAS	FCO
First Order					
Controlling for	ECO		0.41 (0.1)	−0.32 (0.2)	−0.09 (0.4)
	SE	0.57 (0.09)		0.35 (0.2)	−0.22 (0.4)
	BAS	0.87 (0.06)	0.84 (0.01)		0.37 (0.2)
	FCO	0.87 (0.06)	0.83 (0.01)	0.45 (0.2)	
Second Order					
Controlling for	ECO SE			−0.16 (0.4)	−0.21 (0.4)
	BAS FCO	0.85 (0.02)	0.82 (0.02)		

Figures in parentheses indicate statistical significance (p-values) of the respective correlation coefficient.

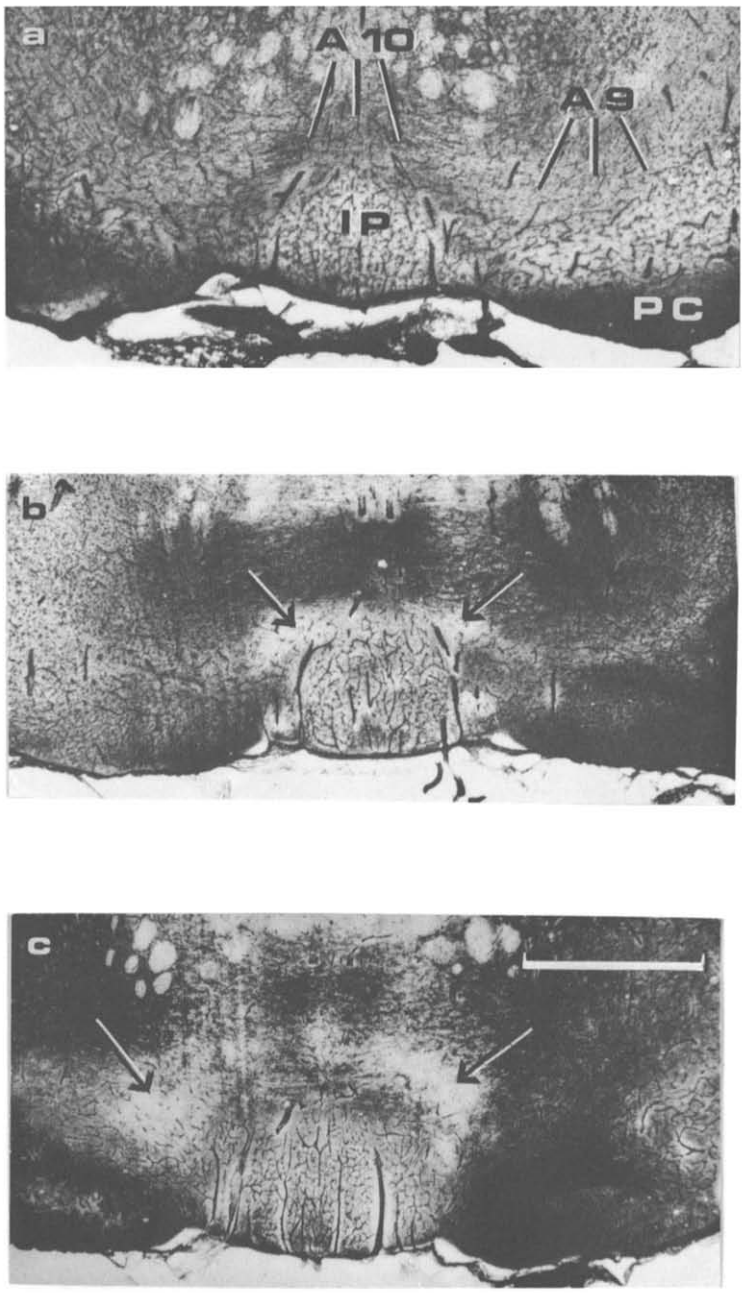

FIG. 3. Coronal sections of the midbrain of tree-shrews injected with 6-OHDA into the VTA (Fink-Heimer impregnation). The pictures show the A10 region and surrounding areas: A9 Substantia nigra; IP N. interpeduncularis; PC Pedunculus cerebri. The bar in c indicates 1 mm. Areas of cell loss are discernable by less coloration (arrows). Using higher magnification none or only a few cells can be detected in these areas. a: Animal G 31 with no obvious cell loss (septal THY-activity 56 nmol/g/hr). b: Animal P1/9 with moderate cell loss (septal THY-activity 138 nmol/g/hr). c: Animal P1/7 with considerable cell loss (septal THY-activity 19 nmol/g/hr).

behavioral measurement out of three items ("eat," "enter," "leave") with four independent neurochemical parameters (THY-activity in target regions, HTH, CO, HIP) is valid. Since only the significantly correlating "eat"-item was punished and not the items "leave" and "enter," this result is also reasonable from a behavioral point of view.

The zero order correlation already showed that THY-activity of one of the target regions of A10, the ACC, does not correlate with the passive avoidance reaction. Partial correlation analysis revealed that the THY-activity in the FCO and BAS was also not significantly involved in the acquisition or performance of passive avoidance behavior.

Although FCO is shown to participate in state-dependent learning and state-dependent alternation [4, 12, 33], we feel in accordance with other authors [16, 22, 35] that the FCO is not crucial for passive avoidance behavior.

As shown in prior work [26], BAS lesions impair performance in avoidance tasks. To our surprise a significant involvement of BAS was ruled out by our statistical treatment of the data. A clear effect of the DA-synapses in the ECO and SE could be demonstrated. These findings, however, are in accordance with a bulk of literature concerning passive avoidance deficits after lesion and stimulation in these brain areas [1, 5, 13, 16, 21, 23, 29, 30, 31].

As THY is present in dopaminergic and noradrenergic neurons, participation of noradrenaline in the behavioral mechanism of passive avoidance is possible. There is, however, suggestive support that the failure of passive avoidance is primarily influenced by dopaminergic synapses [20]. Antagonists of dopamine interfere with the performance of passive avoidance [14,15]. Peripheral application of l-dopa, a precursor of DA and norepinephrine, improves the acquisition of a passive avoidance task, if given prior to punishment [19]. The destruction of the ascending fiber projection from the locus coeruleus, a principal source of noradrenergic innervation in the forebrain, however, does not influence passive avoidance behavior [20].

Subordinate tree-shrews successfully coping with social conflict show an increase of THY-activity in the septal area compared to singly housed animals. These animals evade conflicts by passive avoidance. Contrary to these, subordinates which do not develop a successful coping strategy show a decrease of THY-activity in this brain area. These data indicate that an impairment in the function of the mesolimbic dopaminergic system also occurs under natural conditions and thus prevents the animal from effectively coping with social conflicts [27]. These previous findings and our present results both indicate a crucial role of the septal area and its mesolimbic innervation for coping processes of this kind. The dopaminergic innervation of other target regions of A10 seems to be of minor importance in this respect.

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