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Partial lesion of the dopaminergic innervation of the ventral striatum induces "depressive-like" behavior of rats

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Abstract:
Depression is a frequent comorbid disorder in Parkinson's disease (PD) which may precede appearance of its motor symptoms by several years. Pathomechanisms underlying PD have been suggested to be responsible for the PD-related depression.
The aim of the study was to examine the influence of a partial lesion of striatal dopaminergic terminals on the "depressive-like" behavior of rats in the forced swimming test (FS). 6-Hydroxydopamine (6-OHDA) was injected bilaterally into the ventro-lateral region of the caudate-putamen (CP) (3.75 μg/2.5 μl/side). The locomotor activity and behavior of rats in the FS were measured 2 and 4 weeks after the operation. The lesion extent was analyzed by biochemical and immunohistochemical methods.
Two weeks after the operation, the 6-OHDA-treated rats displayed a prolonged immobility in the FS. This effect disappeared after 4 weeks. The locomotor activity was not influenced by 6-OHDA. Levels of dopamine, DOPAC and HVA were decreased in the nucleus accumbens (NAC) 2 weeks after 6-OHDA but were not changed in the CP, frontal cortex (FCX) and substantia nigra (SN). No significant effect of 6-OHDA on tyrosine hydroxylase-immunoreactivity in the CP and NAC were found.
The present study indicates that a relatively small lesion of dopaminergic terminals in the ventral striatum, which does not produce any motor disturbances, may induce "depressive-like " symptoms.

Key words:
ventral striatum, forced swimming test, 6-OHDA, rat, depression, Parkinson's disease

Abbreviations: 6-OHDA – 6-hydroxydopamine, BG – background, CP – caudate-putamen, DA – dopamine, DL – dorsolateral caudate-putamen, DM – dorso-medial caudate-putamen, DOPAC – 3,4-dihydroxyphenylacetic acid; FCX – frontal cortex; FS – forced swimming test, HPLC – high pressure liquid chromatography, HVA – homovanillic acid, NA – noradrenaline, NAC – nucleus accumbens, OD – optical desity, PD – Parkinson's disease, SN – substantia nigra, TH – tyrosine hydroxylase, TH-ir – tyrosine hydroxylase immunoreactivity, TOD – total optical density, VL – ventro-lateral caudate-putamen, VM – ventro-medial caudate-putamen

Introduction

Primary motor symptoms of Parkinson's disease (PD) (bradykinesia, muscle rigidity, tremor) result from massive degeneration of dopaminergic neurons of the nigrostriatal pathway and a dramatic decrease in the dopamine level in the putamen and caudate nucleus [10]. However, it is generally accepted that the clinical phase of PD is preceded by a preclinical period

lasting several years before motor symptoms appear [20, 27]. Recent neuroimaging studies measuring the binding of radioligands to dopamine transporter have indicated that at the very early clinical stages of PD the density of dopaminergic terminals in the putamen decreases by 60–65% [31, 32]. PD is a multisystem disorder where neuropathological degenerative processes develop in different brain regions starting in the olfactory bulbs, medulla oblongata, pons, and progress to the mesencephalon, limbic system and primary motor areas of the neocortex [2]. During the preclinical period of PD some non-motor prodromal symptoms: autonomic disturbances, olfactory dysfunctions, depression and sleep disorders, may occur [20, 27]. A strong positive association has been found between depression and subsequent incidence of PD [11, 16, 28]. Depressive symptoms, including major depression, are frequently comorbid in 20–70% of advanced PD patients and have a great impact on their quality of life [8, 15, 17, 27, 30]. The above findings indicate that depression in PD may result directly from pathomechanisms underlying progression of this disease and may be used to predict subsequent development of motor symptoms. However, mechanisms underlying depression in PD have not been determined precisely, yet, degeneration and dysfunctions of dopaminergic meso-striatal/cortico/limbic, serotonergic and noradrenergic systems have been proposed to be involved [4, 21, 24, 25].

Clinical observations have been confirmed by animal studies which showed an appearance of "depressive-like" behavior in rats whose dopaminergic systems were lesioned with toxins: 6-hydroxydopamine (6-OHDA), MPTP, rotenone or lipopolysaccharide (LPS) injected either into the striatum or substantia nigra, as measured in the forced swimming (FS), sucrose preference or learned helplessness tests [3, 26, 29, 35]. Since the intrastructural injections of the aforementioned toxins did not impair motor abilities of animals their behavioral effects seemed to result purely from emotional disturbances [3, 26, 29]. MPTP administered systemically in rats has also been reported to lower preference for sucrose over water, to increase immobility in the FS and to induce sleep disorders. However, the latter injection, which modeled the clinical, advanced stage of PD, additionally caused suppression of locomotion and rearing in an open field test and a decrease in daily liquid consumption, which could contribute to the measurements carried out in the above tests and weaken their interpretation in terms of "depressive-like symptoms" [14, 18].

The aim of the present study was to examine whether bilateral 6-OHDA injections into the ventro-lateral region of the caudate-putamen (CP) in a very low dose in rats induce the "depressive-like behavior" measured in the FS. The ventro-lateral CP is accepted to be an equivalent of the putamen in primates and humans – the structure the most severely affected in PD. Therefore, lesions of this region have been considered to model mechanisms of PD in the most appropriate way [9]. The dose of 6-OHDA chosen in the present study was lower than those used previously by others [3, 29, 35] in order to produce a small, well-defined lesion, which would not result in disturbances in locomotor activity of rats and can be a model of depression in pre-clinical stages of PD.

Materials and Methods

Animals

The experiments were carried out in compliance with the Animal Experiments Bill of January 21, 2005; (published in Journal of Laws no. 33/2005 item 289), and according to the NIH Guide for the Care and Use of Laboratory Animals. They received also an approval of Local Ethical Committee. All efforts were made to minimize the number and suffering of animals used.

Male Wistar rats weighing 300–360 g prior to experiments were kept on a light/dark cycle (12/12 h; the light on from 7 a.m. to 7 p.m.) with free access to food and water. All experiments were carried out during the light period.

Operations

Under the pentobarbital anesthesia (Vetbutal, Biowet, Poland; 25 mg/kg, *ip*) the animals were fixed into the stereotaxic instrument (Stoelting, USA) and injected bilaterally with 6-hydroxydopamine (6-OHDA HBr (Sigma-Aldrich, Poland); 3.75 g (free base)/2.5 µl per side, dissolved in a 0.2% ascorbic acid solution) or with solvent into the ventro-lateral region of the CP (AP: 1.2 mm, L: ± 3.1 mm, V: 7.0 mm from bregma according to Paxinos and Watson's atlas [19]. The injection cannulae were left in place for 60 s to enable full absorption of the solution. In order to spare noradrenergic terminals, desipramine (Sigma-Aldrich, Poland) was administered in a dose of 15 mg/2 ml/kg

ip 30 min before 6-OHDA injections. To avoid infections, the rats received an antibiotic (Lincospectin, Pharmacia, Belgium) 24 h before the operation, on the day of operation and 24 h afterwards.

Behavioral observations

Actometers

Locomotor activity of animals was measured by automatic, computerized actometers for small laboratory animals (ACTIFRAME-SYSTEM, GERB Elektronik GmbH, Berlin; designed in co-operation with Dr J. Wolffgramm and Dr G. Schulze, Institute for Neuropsychopharmacology, Free University of Berlin, Germany) 14 or 28 days after brain operations. Each actometer consisted of a Plexiglas cage (40 × 40 × 25 cm) placed inside two layers of frames bearing 16 × 16 transmitters/sensors (in X and Y direction) of infrared beams. Transmitters/sensors of the lower frame were located 4.5 cm and those of the upper one 16.5 cm above the floor of the cage, respectively. The lower frame allowed for measurements of horizontal activity and the upper one – vertical activity of rats. The ACTIFRAME-SYSTEM was connected with a PC equipped with a program (ARNO, developed by Dr J. Wolffgramm, Institute for Neuropsychopharmacology, Free University of Berlin), which analyzed raw data. The following behavioral parameters were evaluated during each 60-min session: 1) a total distance travelled (mean cm per minute), 2) a number of rearing episodes (mean per minute), 3) resting time, when an animal did not execute any locomotor movements. Stationary movements were allowed. This parameter represented the mean duration of all resting periods which started during the analyzed interval.

Forced swimming test

Rats were put individually into a transparent cylindrical tank of 35 cm in diameter and 50 cm in hight filled with tap water at 25 ± 1°C (25 cm deep). The experiment consisted of two sessions: a pre-test (14 or 28 days after operations) and the proper test performed 24 h later (15 or 29 days after operations) which lasted 15 and 5 min, respectively. During the test the rat's behavior was observed and the time of immobility, climbing and swimming was measured. A rat was regarded as immobile when floating motionless or making only small adjustment movements necessary to keep its head above the water. Climbing was recorded when vigorous movements with forepaws directed against the wall of the tank – in and out of the water were displayed. Swimming was defined as horizontal movements of an animal around the tank. Besides the above-mentioned behaviors, animals spent some time on diving, head shaking, or keeping vertical position by relatively big and quick movements of fore- and hind limbs.

Biochemical analyses

Tissue dissection

One day after the completion of behavioral experiments (16 or 30 days after operations) rats were killed by decapitation. Their brains were rapidly removed and dissected along the midline into right and left sides. The left side of the brain was put on a chilled plate and the caudate-putamen (CP), nucleus accumbens (NAC), frontal cortex (FCX) and substantia nigra (SN) were dissected. The tissues were immediately frozen and stored at –80°C until further procedures were applied.

HPLC

Tissue samples were weighted and homogenized in ice-cold 0.1 M perchloric acid. Then, homogenates were centrifuged at 10,000 × g, supernatants were filtered through membrane filters (0.1 μm pore size) and were injected into HPLC system for determination of tissue level of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and noradrenaline (NA). The turnover rate of DA was measured by ratios of its metabolites to the parent compound. Chromatography was performed using a Dionex P580 pump (USA) (flow rate = 0.7 ml/min, Hypersil-Gold C18 analytical column (3 × 100 mm, 3 μm, Thermo Electron Corp., UK) and an LC-4C amperometric detector with a cross-flow detector cell (BAS, IN, USA). The applied potential of a 3 mm glassy carbon electrode was +600 mV with a sensitivity of 5 nA/V. The mobile phase was composed of 0.1 M potassium dihydrogen phosphate (adjusted to pH = 3.5 with orthophosphoric acid), 0.5 mM EDTA, 80 mg/l 1-octanesulfonic acid sodium salt, and a 4% methanol. The chromatographic data were processed by Chromax 2005 (Pol-Lab, Warszawa, Poland) software run on a personal computer.

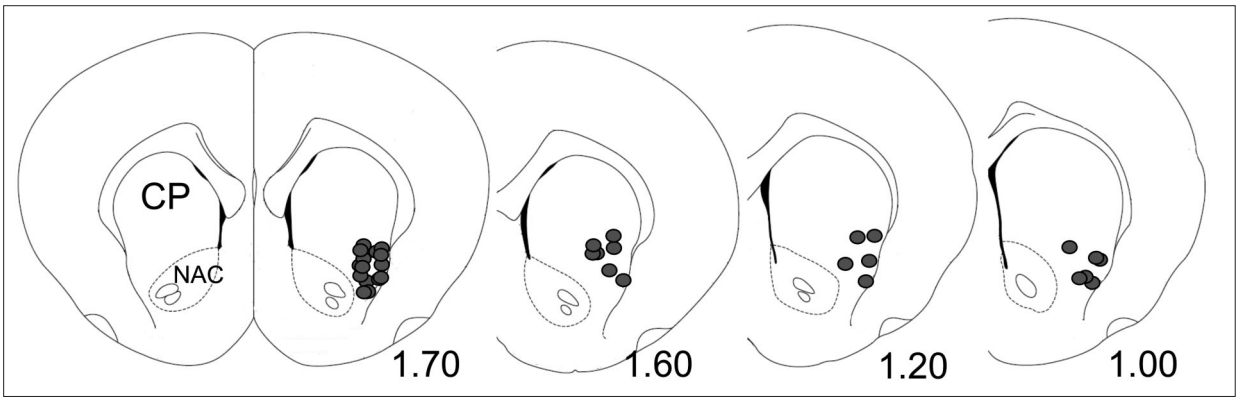

Fig. 1. Localization of cannula tips in frontal sections of the rat caudate-putamen (CP) in reference to bregma according to Paxinos and Watson [19]. Circles indicate cannulae tips. Numbers indicate anterior planes in mm from the bregma. NAC – nucleus accumbens

Histological analyses

Tissue preparation and staining

Right sides of the brains were fixed in cold 4% paraformaldehyde for 7 days and cryoprotected in 20% sucrose solution in phosphate-buffered saline (PBS) for at least 5 days. The brains were then cut on a freezing microtome into 30 μm frontal sections between AP = 2.4 to 0.6 mm from bregma, according to Paxinos and Watson [19]. Series of sections for each group consisted of every 6th section from each brain. They were cryoprotected in 30% sucrose and 30% ethylene glycol in PBS and kept at –20 °C until further analysis. The first series of free-floating sections was incubated for 48 h at 4°C in primary antibodies [mouse anti-tyrosine hydroxylase, 1:3000; Chemicon Int.; Millipore, USA], rinsed in PBS, then incubated for 30 min in secondary antibodies (anti mouse biotinylated, 1:200, Vector Laboratories, UK) and processed using an ABC-peroxidase kit (Vector Laboratories, UK) and 3,3'-diaminobenzidine as a chromogen. The second series of sections was stained with 1% cresyl violet (Sigma-Aldrich, Poland). The stained sections were dried, dehydrated, cleared in xylene and cover-slipped in a Permount medium (Fisher Scientific, USA).

Verification of the placement of cannulae tips

Placements of cannulae tips were examined on striatal slices stained with cresyl violet and/or tyrosine hydroxylase-immunoreactive (TH-ir) (Fig. 1) using an image analysis system equipped with a camera (MCID, St. Catharines, Ontario, Canada).

Densitometric estimation of the TH-ir

The optical densities (OD) of slices stained for TH-ir were analyzed with computer-assisted densitometry using an image analysis system (MCID, St. Catharines, Ontario, Canada). The whole CP and NAC on each slice were outlined and divided into the following regions: dorso-lateral CP (DL), ventro-lateral CP (VL), dorso-medial CP (DM), ventro-medial CP (VM), core and shell of NAC (Fig. 2C). The mean total optical density (TOD) for each subregion was measured. The background (BG) was measured in the region of the corpus callosum. The values of OD (in arbitrary units) for each subregion were obtained by subtracting the BG from the TOD on each section. The results were averaged for all slices from the animal.

Statistics

The results of locomotor activity were analyzed by ANOVA for repeated measures and LSD *post-hoc* test. The data of the FS and biochemical data were analyzed by one-way ANOVA. All statistical calculations were done using STATISTICA 7.0 Software (Statsoft, Inc. USA).

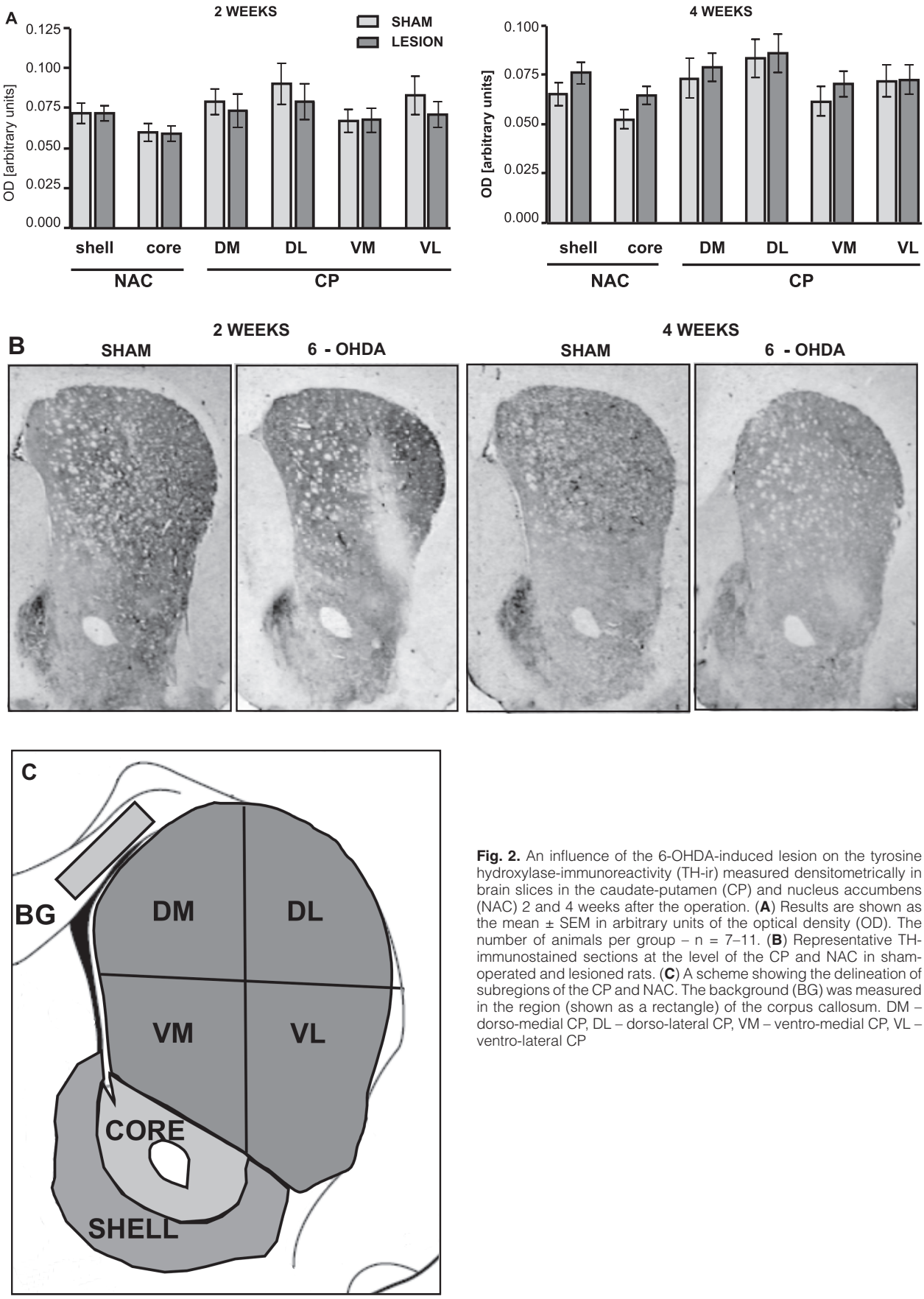

Fig. 2. An influence of the 6-OHDA-induced lesion on the tyrosine hydroxylase-immunoreactivity (TH-ir) measured densitometrically in brain slices in the caudate-putamen (CP) and nucleus accumbens (NAC) 2 and 4 weeks after the operation. (**A**) Results are shown as the mean ± SEM in arbitrary units of the optical density (OD). The number of animals per group – n = 7–11. (**B**) Representative TH-immunostained sections at the level of the CP and NAC in sham-operated and lesioned rats. (**C**) A scheme showing the delineation of subregions of the CP and NAC. The background (BG) was measured in the region (shown as a rectangle) of the corpus callosum. DM – dorso-medial CP, DL – dorso-lateral CP, VM – ventro-medial CP, VL – ventro-lateral CP

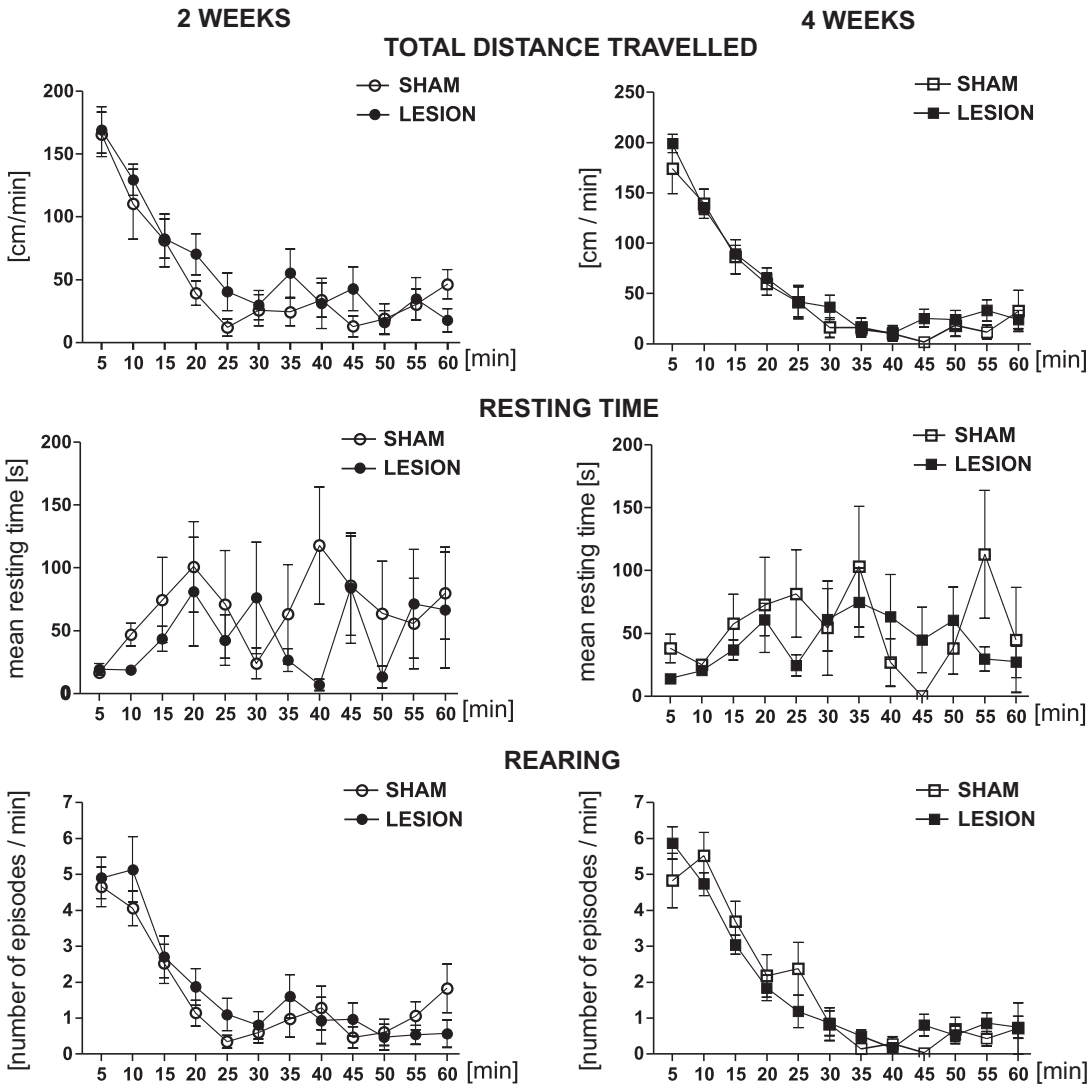

Fig. 3. An influence of the 6-OHDA-induced lesion on locomotor activity of rats measured in actometers 2 and 4 weeks after the operation. Results are shown as the mean ± SEM. Abscissas – time after the beginning of testing. The number of animals per group – n = 7–11

Results

Behavioral observations

Actometers

6-OHDA administered bilaterally into the CP did not influence locomotor activity of rats, when measured 2 and 4 weeks after the operation. No difference between 6-OHDA-treated and sham-operated rats was found with regard to the total distance travelled, number of rearing episodes and resting time during the 60-min experiment (Fig. 3).

FS

6-OHDA administered bilaterally into the CP prolonged the immobility time, but did not influence the time of climbing and swimming, when measured 2 weeks after the operation. Four weeks after the operation, no influence of the lesion on the behaviors measured in the FS was noted (Fig. 4).

Histological analyses on the right side of the brain

Histological analysis showed that cannulae tips were localized mainly in the CP VL (Fig. 1).

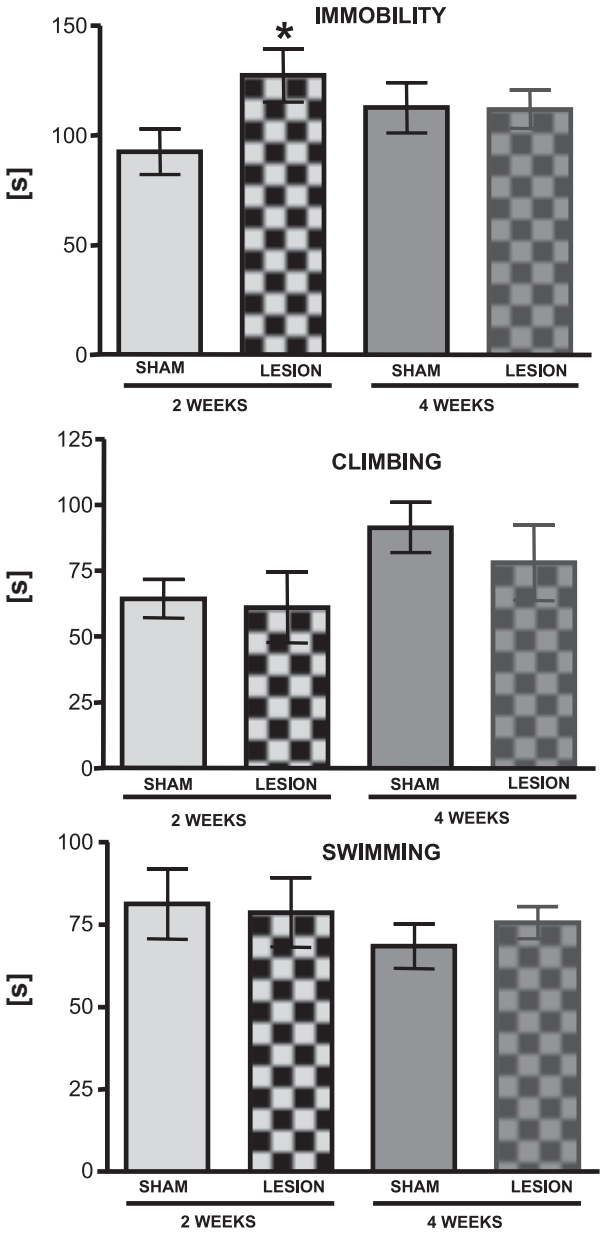

Fig. 4. An influence of the 6-OHDA-induced lesion on behavior of rats measured in the forced swimming test (FS) 2 and 4 weeks after the operation. Immobility, climbing and swimming were measured as the time spent on a respective behavior during a 5-min observation period. Results are shown as the mean ± SEM. The number of animals per group – n = 7–11. Asterisk – a statistically significant ($p < 0.05$) difference *vs.* sham-operated animals (one-way ANOVA)

Densitometric analysis of TH-ir in the CP and NAC did not discover any statistically significant influence of 6-OHDA on this parameter 2 or 4 weeks after the operation (Fig. 2A), although a small decrease in staining along the cannula track and in the surroundings of its tip was visible (Fig. 2B).

Biochemical analyses of DA, its metabolites and NA in the CP, NAC, SN and FCX on the left side of the brain

6-OHDA administered into the CP did not influence levels of DA, DOPAC and HVA in this structure or in the SN and FCX 2 and 4 weeks after the operation (Fig. 5). In contrast, levels of DA, DOPAC and HVA were lowered in the NAC by 61%, 63%, 64%, respectively, only 2 but not 4 weeks after the operation (Fig. 5). Levels of NA in all structures examined (CP, NA, SN, FCX) were unchanged, when measured at the two above mentioned time points (Fig. 5).

Discussion

The present results show that the lesion induced by 6-OHDA injections in the ventro-lateral region of the CP in rats prolonged immobility time measured in the FS 2 weeks after the operation but did not influence the locomotor activity of animals.

The immobility time measured in the FS test is commonly regarded as a "depressive" sign in animals. In this test an animal is exposed to "life-threatening" conditions, learns that it is not able to escape from the tank filled with water, resigns from the struggle and freezes immobile. The latter behavior may resemble depressive reaction of humans to an extensive stress. Since 1977, when the test has been described by Porsolt et al. [23], a number of data have shown that the immobility time is reversed by antidepressant drugs belonging to different classes [7, 22, 34] which supports its value as a model of depressive symptoms. However, execution of the test is dependent on motor ability of an animal, among other things. Therefore, in order to exclude a potential influence of motor disturbances of rats on their performance of the FS test, we examined their locomotor activity in very sensitive actometers. We did not find any influence of the 6-OHDA lesion on different measured parameters (total distance travelled, number of rearing episodes and resting time), which seems to support the idea that the increase in the immobility time in the FS in lesioned animals resulted from their state of "despair". The above mentioned behavior was observed 2 weeks but disappeared by 4 weeks after the operation.

Careful examination of the lesion extent in 6-OHDA-treated rats showed a very small decrease in the TH

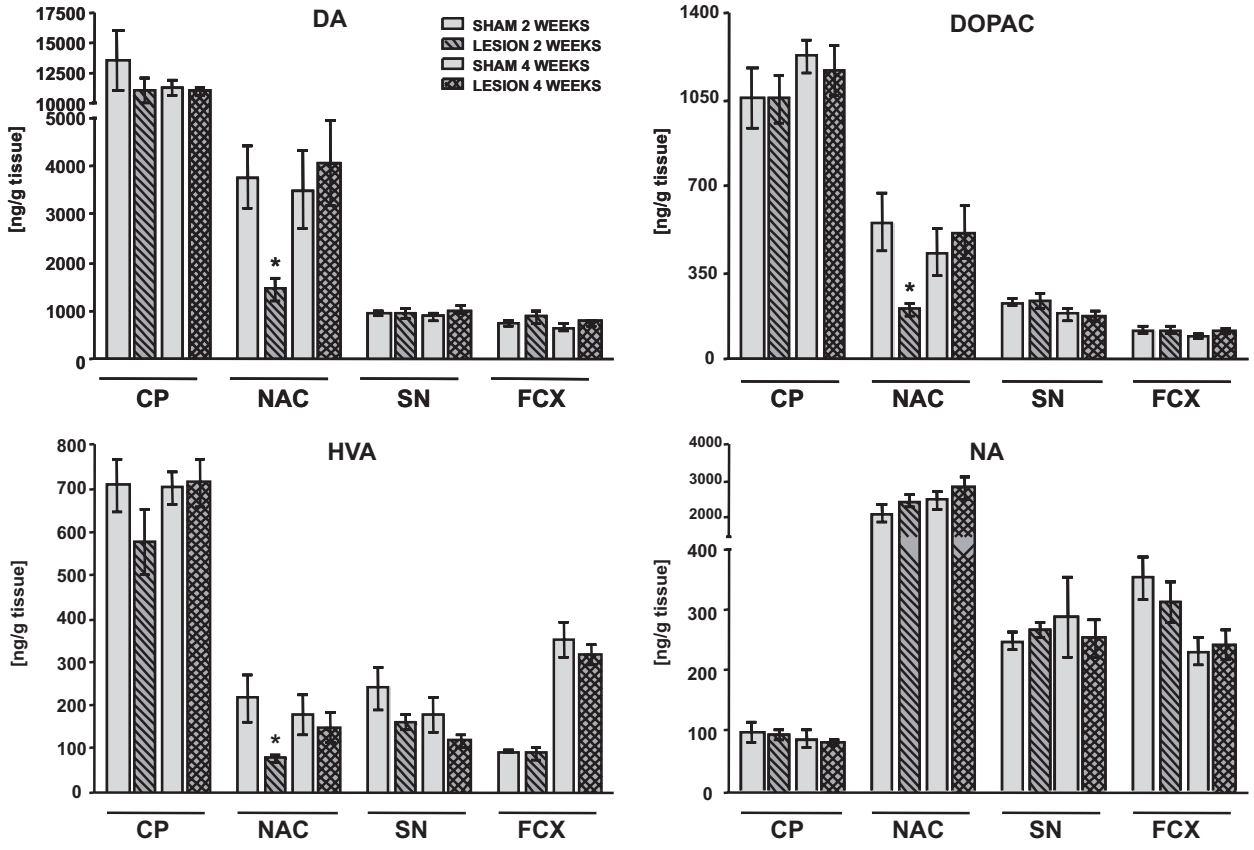

Fig. 5. An influence of the 6-OHDA-induced lesion on the levels of dopamine (DA) and its metabolites DOPAC and HVA, as well as noradrenaline (NA) in different brain structures, measured 2 and 4 weeks after the operation. CP – caudate-putamen, FCX – frontal cortex, NAC – nucleus accumbens, SN – substantia nigra. Results are shown as the mean ± SEM. The number of animals per group – n = 7–11. Asterisk – a statistically significant ($p < 0.05$) difference *vs.* sham-operated animals (one-way ANOVA)

immunoreactivity (the rate-limiting enzyme of DA synthesis) along the cannula track and in the surroundings of its tip that did not result in any statistically significant difference either in the CP or NAC. Interestingly, 6-OHDA injections induced a ca. 60% decrease in DA, DOPAC and HVA levels in the NAC 2 but not 4 weeks after the operation. These results may suggest that 6-OHDA disrupted the mesolimbic dopaminergic innervation of this structure, which paralleled in time an increase in the immobility time in the FS, although no clear evidence for its structural damage was found. It may be supposed that the above lesion was compensated for between 2 and 4 weeks after the operation. The development of compensatory mechanisms in response to the 6-OHDA-induced degeneration (especially when the lesion is moderate) is a well known phenomenon and could be based on an increase in the DA synthesis in – and release from – surviving dopamine cells, reduced rate of DA inactivation, sprouting of axon collaterals [5, 6, 9, 36], and other processes.

Interestingly, in the present study no changes in the turnover rates were found either in the CP or NAC (data not shown), hence, some changes in terminal density, sprouting, expression and activity of TH are more probably compensatory mechanisms rather than alterations in activity of DA metabolizing enzymes.

PD is an age-related neurodegenerative disease. However, in the present study the dopaminergic toxin was administered in young animals which is a generally accepted procedure [3, 26, 29, 35], but may be considered as weakness of the model. This could be the main reason of the development of efficient compensatory mechanisms which masked both the neurochemical and behavioral effects of the lesion.

In spite of the fact that tips of our injection cannulae were directed into ventro-lateral region of the CP we did not find any statistically significant differences in the level of DA and its metabolites in this structure

or in the structure of origin of its dopaminergic innervations, i.e., the SN. It may be concluded that the toxin solution diffused from cannula tips mainly in the ventro-medial direction towards the NAC. Moreover, it cannot be excluded that at least a part of the ventral region of the CP was excised during sectioning of the tissue and then analyzed together with the NAC. On the other hand, we did not divide the whole CP into smaller regions for HPLC analysis and, therefore, any potential biochemical alterations confined to its most ventral part could be attenuated.

In the present study the administration of 6-OHDA was preceded by a systemic injection of desipramine. This regimen was intended to destroy only dopaminergic terminals but to spare noradrenergic ones. Our biochemical analysis confirmed that 6-OHDA did not influence the NA level in regions located close to the cannulae tips (CP, NAC), as well as in distant structures (SN, FCX). These results supported the view that a selective lesion of dopaminergic innervations was sufficient to trigger "depressive-like" behavior in rats.

NAC together with the most ventral part of the CP and the striatal elements of the tubercle olfactory, belongs, to the so-called "ventral striatum" – a region associated with limbic structures, such as the amygdala, hippocampus, midline thalamus and certain regions of the prefrontal cortex. "Ventral striatum" is strongly innervated by dopaminergic mesolimbic pathway arising from the ventral tegmental area and projects back to the latter structure [1, 12, 33]. Anatomical connections with the limbic system make the above region functionally strongly associated with emotional and motivational aspects of behavior [12]. Ventral striatum has been postulated to be crucial for depression appearing in PD, since a negative correlation has been found between the binding of radioligand to dopaminergic and noradrenergic transporters ([^{11}C]RTI-32) in this region and depression in PD patients [25].

The present study supports the importance of the lesion of dopaminergic innervations of this region for "depressive-like" symptoms in the animal model. In agreement with this view, the dopaminergic lesion of the NAC has been found to suppress an "antidepressive-like" effect of desipramine in the FS in rats [13]. Moreover, Winter et al. [35] reported the presence of an association between "depressive-like" disturbances observed in the learned-helplessness test and the magnitude of the ventral tegmental area lesion.

Summing up, our present study seems to support the view that already a small lesion of dopaminergic terminals in the ventral striatum, which may reproduce preclinical stages of PD, induces "depressive-like" behavior in rats. These results may imply that depression in PD is not only a psychological reaction to motor disability of patients but results directly from pathomechanisms of this disease.

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