



## Research paper

## Lesions of the lateral habenula improve working memory performance in hemiparkinsonian rats

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## ABSTRACT

The lateral habenula (LHb) is an important structure involved in various brain functions, because it controls the activity of dopaminergic and serotonergic systems in the midbrain. The impairment of working memory commonly occurs in Parkinson's disease; however, it is not clear whether the LHb involves in the regulation of working memory in rats with unilateral 6-hydroxydopamine lesions of the medial forebrain bundle (MFB). In this study, we found that the MFB lesions in rats decreased choice accuracy as measured by the T-maze rewarded alternation test compared to control rats, indicating the induction of working memory impairment, and decreased dopamine (DA) levels in the medial prefrontal cortex (mPFC), hippocampus and amygdala. Further, rats in the MFB and LHb lesion group showed increased choice accuracy compared to rats in the MFB lesion group, indicating the enhancement of working memory after lesioning the LHb. Neurochemical results found that lesions of the LHb increased DA levels in the mPFC, hippocampus and amygdala in the MFB and LHb lesion group, as well as serotonin (5-HT) level in the mPFC. These findings suggest that DA depletion plays a key role in working memory impairment, and lesions of the LHb improve working memory in the MFB-lesioned rats, which involves in increases in the levels of DA and 5-HT in the mPFC, hippocampus and amygdala. Additionally, the present results may have implications for improving our understanding of the neuropathology and/or treatment of PD.

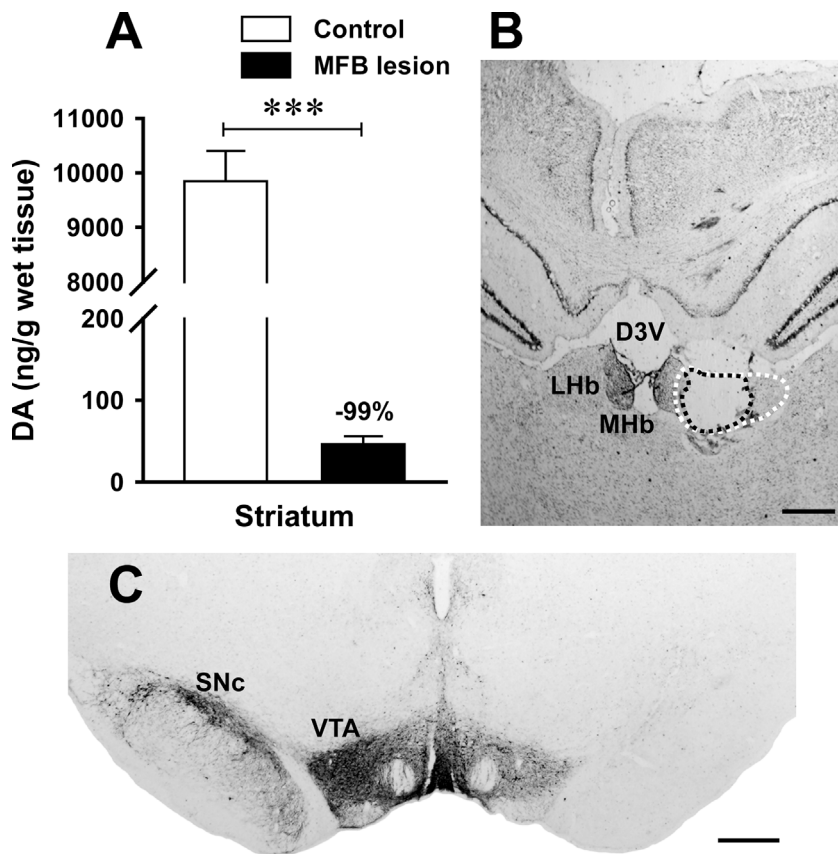
## 1. Introduction

Parkinson's disease (PD) has typically been considered to be a motor disorder secondary to degeneration of the nigrostriatal dopaminergic pathway. However, non-motor symptoms including neuropsychiatric and cognitive deficits are now more recognized, and are widespread in PD [1]. Patients with PD may express a variety of cognitive dysfunctions such as impairments in executive function and memory, and dementia [2]. In previous experimental studies, the results of cognitive behaviors in 6-hydroxydopamine (6-OHDA)- and 1-Methy-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned rats were inconsistent. These studies reported cognitive impairments or unchanged cognitive behaviors in different rat models of PD [3–12]. Recently, our studies have found that unilateral 6-OHDA lesions of the medial forebrain bundle (MFB) in rats induce working and hippocampus-dependent memory impairments [13,14], suggesting that dopamine (DA) depletion plays an important role in cognitive deficits.

The lateral habenula (LHb) is an epithalamic structure, and neurons in the structure are almost uniformly glutamatergic [15]. It receives limbic and motor signals from diverse forebrain regions and projects

mainly to dopaminergic and serotonergic nuclei in the midbrain [16,17]. Based on its prominent connections with the monoaminergic systems, the LHb is known to be involved in a wide range of brain functions and clinical disorders [18,19]. Further, accumulating evidence in rodents and humans strongly implicates a role in cognition as one of the functions of the habenula, because the studies have found that the LHb shows decreased metabolic activity in aged memory impaired rats [20] and memory impairment in rats with lesions of the habenula [21], and the functional impairment of the habenula correlates with impaired cognitive performance in patients with schizophrenia [22]. Additionally, several studies have also found an increase in the firing activity of LHb neurons in rats with unilateral 6-OHDA lesions of the substantia nigra pars compacta (SNc) [23,24]. However, little is known about the role of the LHb in the regulation of working memory in parkinsonian animals. Therefore, the current study aimed to examine (i) effect of LHb lesions on working memory by the T-maze rewarded alternation test in rats with unilateral 6-OHDA lesions of the MFB, and (ii) how lesions of the LHb affect DA and serotonin (5-HT) levels in the medial prefrontal cortex (mPFC), hippocampus and amygdala that are involved in learning and memory processes.

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**Fig. 1.** Histological verification of electrical lesions of the LHB and DA level in the striatum. MFB-lesioned rats showed decreased DA level in the striatum compared to control rats (A). Photomicrograph of cresyl violet staining showing LHB lesion from rat in the MFB and LHB lesion group (right; B). Photomicrograph of TH immunostaining showing the Snc dopaminergic neurons degeneration from rat in the MFB lesion group (right; C). \*\*\* $P < 0.001$  vs. control rats, unpaired Student's  $t$ -test;  $n = 7$ – $8$  rats/group; data are expressed as mean  $\pm$  SEM. Scale bars: B, C = 500  $\mu$ m. D3 V, dorsal 3rd ventricle; MHb, medial habenula; ventral tegmental area, VTA.

## 2. Methods and materials

### 2.1. Animals and drugs

Male Sprague–Dawley rats weighing 270–320 g at the time of surgery were used. All rats were cared for and used in accordance with the National Institutes of Health guidelines for the care and use of experimental animals, and all procedures were approved by the Animal Care and Use Committee of the University. The rats were randomly divided into four groups: normal rats as control, MFB-lesioned rats (MFB lesion), MFB- and LHB-lesioned rats (MFB + LHB lesion), and MFB-lesioned and LHB sham-lesioned rats (MFB lesion + LHB sham). Desipramine hydrochloride, 6-OHDA hydrochloride and apomorphine hydrochloride were obtained from Sigma-Aldrich (MO, USA). 6-OHDA and apomorphine were prepared in saline containing 0.02% ascorbic acid; desipramine was dissolved in saline.

### 2.2. Unilateral 6-OHDA lesions in the MFB

As previously described [13], 30 min before surgery, rats were injected with desipramine (25 mg/kg, i.p.) to protect noradrenergic neurons, and then received 6-OHDA (12  $\mu$ g/4  $\mu$ l) lesions of the right MFB (AP:  $-4.4$  mm, ML: 1.2 mm, DV: 7.8 mm relative to bregma) to destroy dopaminergic neurons [25]. One week after surgery, rats were given apomorphine (0.05 mg/kg, s.c.) and those exhibiting more than 20 contralateral turns per 5 min were selected for further experiments [13].

### 2.3. Unilateral electrical lesions of the LHB

Two weeks after the injection of 6-OHDA into the right MFB, the 6-OHDA-lesioned rats received a direct current delivery of 0.5 mA for 10 s through an electrode inserted into the right LHB (AP:  $-3.7$  mm, ML:

0.7 mm, DV: 4.5 mm relative to bregma) [25], as previously described [26]. For sham-lesioned rats, the electrode was inserted at the same coordinates for the same amount of time, but no current was passed. After surgery, rats were allowed to recover for one week before the experiments.

### 2.4. Behavioral tests

All behavioral tests were performed during the fourth week after 6-OHDA into the MFB. These tests were done in an isolated room between 8:00 and 12:00 am, and the activity of each rat was recorded by a digital video camera (HR-550E, Sony, Tokyo, Japan).

#### 2.4.1. Open-field test ( $n = 8$ – $9$ rats for each group)

To assess effects of 6-OHDA lesions of the MFB and electrical lesions of the LHB on spontaneous locomotor activity, the rats were tested in the open-field (dimensions: 100 cm  $\times$  100 cm) as previously described [13]. Each rat was placed in the center of the open-field, and the number of squares crossed (horizontal locomotion) and of rearings (vertical activity) was observed for 5 min.

#### 2.4.2. T-maze rewarded alternation test ( $n = 8$ – $9$ rats for each group)

T-maze rewarded alternation test is classically used for working memory studies in the rat [27]. The construction of the T-maze and the test procedures were identical to those described in our previous studies [13,14]. Briefly, rats were habituated to a T-maze until they were readily eating chocolate chips placed at the end of each arm and were acclimated to handling in 4 consecutive days. On the following test day, the rat was subjected to a series of 18 trial sessions with 30 s delay between trials. At the start of each trial, the rat was put in the start arm facing a way from the goal arms, and allowed it to choose one goal arm where it received a chocolate pellet, and then a correct choice was scored. If the rat entered the goal arm which was chosen previously, it

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