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Altered neuronal activity in the primary motor cortex and globus pallidus after dopamine depletion in rats ☆

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ABSTRACT

The involvement of dopamine (DA) neuron loss in the etiology of Parkinson's disease has been well documented. The neural mechanisms underlying the effects of DA loss and the resultant motor dysfunction remain unknown. To gain insights into how loss of DA disrupts the electrical processes in the cortico-subcortical network, the present study explores the effects of DA neuron depletion on electrical activity in the primary motor cortex (M1), on the external and the internal segment of the globus pallidus (GPe and GPi respectively), and on their temporal relationships. Comparison of local field potentials (LFPs) in these brain regions from unilateral hemispheric DA neuron depleted rats and neurologically intact rats revealed that the spectrum power of LFPs in 12–70 Hz (for M1, and GPe) and in 25–40 Hz (for GPi) was significantly greater in the DA depleted rats than that in the control group. These changes were associated with a shortening of latency in LFP activities between M1 and GPe, from several hundred milliseconds in the intact animals to close to zero in the DA depleted animals. LFP oscillations in M1 were significantly more synchronized with those in GPe in the DA depleted rats compared with those in the control rats. By contrast, the synchronization of oscillation in LFP activities between M1 and GPi did not differ between the DA depleted and intact rats. Not surprisingly, rats that had DA neuron depletion spent more time along the ladder compared with the control rats. These data suggest that enhanced oscillatory activity and increased synchronization of LFPs may contribute to movement impairment in the rat model of Parkinson's disease.

1. Introduction

The basal ganglia form a complex network that processes cortical information important for movement and cognition [1–3]. Alterations of neuronal activity in the basal ganglia and cortices have been reported in patients with Parkinson's disease (PD) as well as in animal models of PD [4–11]. These changes in neuronal activity are believed to mediate many of the dysfunctional effects seen in PD because they impact the circuits connecting the basal ganglia and the cortex [10,12–14]. However, the specific pathological changes that occur with DA loss in oscillation activity and functional connectivity from the cortex to the basal ganglia remain poorly understood.

The transmission of rhythmic cortical activity from the cortex to the basal ganglia has been studied in anesthetized rats [15,16]. An increase in discharge oscillations at 1 Hz from the basal ganglia is observed in anesthetized rats with unilateral DA depletion. This activity is coherent with the 1 Hz oscillatory firing patterns dominant in the cortex [17,18]. Transmission from the cortex to the basal ganglia has also been studied in rats using electrical stimulation of the motor cortex. After DA depletion, the cortical stimulation induces a long disinhibition in GPe, which is transmitted to GPi and generates an abnormally strong long inhibition in GPi, which then generates a strong and long excitation in the thalamic projection sites that are transmitted to the motor cortex with incorrect information [19,20].

Simultaneous behavioral recordings and chronic microelectrode neural recordings in awake and behaving rodents hold great promise to study the neural bases of behavior and the information transmission between the cortex and the basal ganglia. Some studies suggest that increases in the synchronization between the subthalamic nucleus or substantia nigra to cortex, or the external segment of the globus pallidus facilitate the emergence of special range activity in the cortex after DA loss [10,11,21–23]. These observations led to our general hypothesis that DA neuron loss alters the magnitude of the electrical activities in

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the basal ganglia and enhances its tendency to become entrained by oscillatory activity expressed in the cortex.

The aim of the present study was to determine: a) how DA loss affects LFP activities in the primary motor cortex (M1), the globus pallidus in rodents (an area analogous to the external segment of the globus pallidus in primates, GPe) and the entopeduncular nucleus in rodents (an area analogous to the internal segment of the globus pallidus in primates, GPi) [24,25]. In this paper, we will use the primate terminology for simplification and consistency reasons, and b) how DA loss affects the coherent oscillatory activity at the level of LFPs recorded in M1 with GPe or GPi. LFPs were pair-recorded from chronically implanted electrodes in the M1 and GPe or GPi of rats with unilateral DA neuron lesions, while they were engaged in a locomotor task. Control unilateral recordings in M1 and GPe or GPi were also obtained in neurologically intact rats.

2. Materials and methods

2.1. Animal

All experimental procedures were conducted on male Wistar rats (280–320 g, Animal Center of Shandong University, China). Rats were kept under standard housing conditions at constant temperature (22 ± 1 °C), humidity (relative, 30%), and light/dark 14/10 cycles. Water was available ad libitum. Food intake was limited to 10–20 g/day to maintain constant animal weight. Animal care and surgery were conducted in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals (NIH Guidelines). Every effort was made to minimize the number of animals used and the pains they suffered.

2.2. Behavioral training task

A ladder composed of two clear Plexiglas side walls (100 × 20 cm) with timber rungs (3 mm in diameter) inserted at random distances ranging from 1 to 3 cm was used in the testing. The ladder was elevated 30 cm above the ground with a square wooden case (home cage) at one end. Two weeks prior to surgery, rats were placed at one end of the ladder and trained to walk spontaneously to the home cage. The rats received three training trials each day for 3–7 days, after which they reliably walked to the home cage after being placed at the other end. During the testing, the time to cross the entire length of the ladder was recorded and the number of foot placement errors was determined by a rating system used in previous studies [26,27]. Briefly, 3 points were given when the animal completed or missed a rung and the body fell onto the ladder; 2 points were given when the animal initially stepped on the rungs but slipped off; and 1 point was given when the animal step a paw on a rung but did not place its body weight on that paw. The animals' performance was videotaped by a camera (Logitech AF, Taiwan) positioned at a slight ventral angle which enabled both sides of the body and paw positions to be simultaneously recorded.

2.3. Unilateral lesion of the nigrostriatal pathway

Unilateral 6-hydroxydopamine (6-OHDA) lesion of the dopaminergic nigrostriatal pathway was performed on rats after the behavioral training. Rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and placed in a stereotaxic frame, with body temperature maintained at 37 ± 0.5 °C using a heating pad. The skull was exposed and two holes were drilled on the skull according to appropriate coordinates. Rats were injected with desmethylimipramine (15 mg/kg, i.p.) 30 min prior to the intracerebral infusion to protect noradrenergic neurons. The neurotoxin 6-OHDA (hydrochloride salt; Sigma) was dissolved in ice-cold 0.9% w/v NaCl solution containing 0.02% w/v ascorbate to a final concentration of 4 mg/ml immediately before use. Then 2 μl of 6-OHDA solution was injected into the medial substantia nigra (5.2 mm posterior and 2.1 mm lateral of the bregma, and 8.0 mm ventral to the dura) and 2 μl into the ventral tegmental area (6.8 mm posterior and 0.6 mm lateral of the bregma, and 8.6 mm ventral to the dura). The injection was made at a rate of 0.5 μl/min using a 5-μl microsyringe. After each injection, the micropipette was left in place for an additional 5 min and then slowly withdrawn. The control rats received only the vehicle (0.02% ascorbic acid in physiological saline) at the same coordinates. Rats received post-operative care until wakefulness and were returned to their home cages.

Four weeks after 6-OHDA injection, a rotating behavioral response to apomorphine (0.05 mg/kg, s.c.) test was performed in order to assess the severity of the nigral lesion [28]. Animals that performed at least 80 rotations opposite to the lesioned site within 20 min following the apomorphine treatment were considered animals with successful surgery and only those were used for electrophysiological recordings.

2.4. Recording electrode placement

A headstage adapted from previous studies [29,30] was designed for the recording electrode assembly. Briefly, the headstage composed of a 3-pin box connector socket stripe (2.54 mm, BCSS-1-SV, Indiana, USA) with double nickel–chromium teflon-insulated microwires (California Fine Wire, Grover Beach, CA, USA, 100 μm in diameter). One end of the microwires was stripped by gently scraping off about 2 mm of insulation and tinned with a soldering iron to attach to a pin of the connectors. A copper wire (200 μm in diameter) served as a ground wire was also soldered onto a pin of the connector. After the microwires and ground wire were tightly soldered, Epoxy glue was applied to the base and surrounding of the connector to build onto the headstage a movable driver with recording electrodes. The tip impedance of the electrode was 0.5–0.8 MΩ at 1 kHz.

The headstage was implanted into both intact rats and rats with unilateral DA neuron lesions. The target regions of the headstage were M1 (1.0 mm anterior and 2.0 mm lateral of the bregma, and 0.4 mm ventral to the dura) and GPe (1.0 mm posterior and 3.0 mm lateral of the bregma, and 6.6 mm ventral to the dura) or GPi (2.3 mm posterior and 2.9 mm lateral of the bregma, and 7.7 mm ventral to the dura). Skull screws were used for ground wire connection and fixing the headstage to the skull. Dental cement was then applied to glue the headstage to the skull. The rats were given ketoprofen (Ketofen 2 mg/kg, s.c., Sigma, USA) following surgery and 24 h later again for pain relief. They were allowed at least 7 days to recover before the first recording session.

2.5. Electrophysiological data acquisition

Testing took place 8–10 days after the implantation surgery. Electrophysiological and behavioral recordings were simultaneously performed and displayed on a computer screen for visual inspection. Neural signals were pre-amplified 25 times by a high impedance preamplification device (SWF-2, Chengdu, China) and then amplified by a multichannel bioamplication system (RM6280BD, Chengdu, China) and digitized at a sample rate of 10 kHz with band pass filtered from 0.8 to 300 Hz. The raw signal was stored for further analysis in MATLAB 2010a (The Mathworks, USA) and LFP analysis software 2009 http://www.nottingham.ac.uk/neuronal-networks/ [31].

2.6. Histology

The placement of the recording probes was checked after final testing. Immediately after the rats were given a lethal dose of pentobarbital sodium, electrical microlesion (10 μA, 10 s × 2) was induced by passing an anodal current through the electrode at each recording site. Rats were perfused intracardially with 200 ml saline followed by 200 ml 4% paraformaldehyde and 1% potassium ferricyanide in phosphate buffer solution (PBS). The brain was quickly removed and frozen in an isopentane bath at −80 °C for histological analysis. Coronal brain