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Research Report

Dopamine depletion increases the power and coherence of high-voltage spindles in the globus pallidus and motor cortex of freely moving rats☆

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ABSTRACT

Studies on patients with Parkinson's disease and in animal models have observed enhanced synchronization of oscillations in several frequency bands within and between the cortical–basal ganglia (BG) structures. Recent research has also shown that synchronization of high-voltage spindles (HVSs) in the cortex, striatum and substantia nigra pars reticulate is increased by dopamine depletion. However, more evidence is needed to determine whether HVS activity in the whole cortex–BG network represents homologous alteration following dopamine depletion. As the globus pallidus (GP) is in a central position to propagate and synchronize oscillations in the cortical–BG circuits, we employed local-field potentials and electrocorticogram to simultaneously record oscillations in the GP and primary (M1) and secondary (M2) motor cortices on freely moving 6-hydroxydopamine (6-OHDA) lesioned and control rats. Results showed that HVS episodes recorded from GP, and M2 and M1 cortex areas were more numerous and longer in 6-OHDA lesioned rats compared to controls. Relative power associated with HVS activity in the GP, and M2 and M1 cortices of 6-OHDA lesioned rats was significantly greater than that for control rats. Coherence values for HVS activity between the GP, and M2 and M1 cortex areas were significantly increased by dopamine depletion. Time lag between the M1 cortex HVS and GP HVS was significantly shorter for dopamine depleted than normal rats. Findings indicate a crucial rule for dopamine in the regulation of HVS activity in the whole cortical–BG circuit, and suggest a close relationship between abnormally synchronized HVS oscillations in the cortex–BG network and Parkinson's disease.

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Abbreviations: BG, basal ganglia; DAB, 3,3-diaminobenzidine tetrahydrochloride; ECoG, electrocorticogram; GP, globus pallidus; GPe, external globus pallidus; HVSs, high-voltage spindles; LFP, local-field potential; M1 cortex, primary motor cortex; M2 cortex, secondary motor cortex; MSNs, medium spiny neurons; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; SNr, substantia nigra pars reticulate; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; TH, tyrosine hydroxylase

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1. Introduction

Abnormalities in the synchronization of oscillatory activity are increasingly recognized to be involved in several types of brain dysfunction (Uhlhaas and Singer, 2006). Converging evidence suggests that Parkinson's disease (PD) is accompanied by altered synchronization of oscillations in different frequency ranges (Bergman et al., 1998; Brown, 2003; Leblois et al., 2007). The most significant findings to date relate to oscillations in the 14–30 Hz range, which was often termed as "beta-band activity" in the motor system (Brown and Williams, 2005). Increased synchronization of beta-band activity has been observed between the basal ganglia (BG) nuclei and over cortical motor areas in PD patients (Brown et al., 2001; Cassidy et al., 2002; Kuhn et al., 2004; Levy et al., 2002; Marsden et al., 2001; Weinberger et al., 2006; Williams et al., 2002). Investigations on animals have also shown that the coherence of beta-oscillations over the cortical–BG networks was significantly increased by dopamine depletion (Mallet et al., 2008a, b; Sharott et al., 2005; Williams et al., 2002).

High-voltage spindles (HVSs), which exhibit a characteristic spike-and-wave pattern and an oscillation frequency ranging between 5 and 13 Hz (Dejean et al., 2007), have been reported to spontaneously and widely appear in the cortical–BG networks in rats (Berke et al., 2004; Buzsaki et al., 1988a, b, 1990; Jando et al., 1995; Kaplan, 1985; Magill et al., 2004; 2005; Shaw, 2004). Previous research has shown that interference with striatal dopaminergic transmission can increase the incidence of cortical HVSs, indicating a possible role for dopamine in the modulation of HVSs (Buonamici et al., 1986; Buzsaki et al., 1990; Semba and Komisaruk, 1984). However, little is known about how the synchronization of HVS activity may change in parkinsonism.

Recently, one study exploring signal transmission in the cortex–BG network in rats after dopamine depletion observed a significant enhancement of oscillatory synchronization between the cortex, striatum and substantia nigra pars reticulate (SNr) during HVS episodes (Dejean et al., 2008). As the striatum and SNr respectively act as the main input and output nuclei of the BG (Parent and Hazrati, 1995), we hypothesized that enhanced synchronization of HVS activity may be general for all the cortical–BG nuclei.

The globus pallidus (GP) is in a central position to propagate and synchronize oscillatory activities in the cortical–BG circuits, and has been reported to be critical for orchestrating exaggerated beta oscillation in the circuits associated with PD (Bolam et al., 2000; Kita and Kitai, 1991; Mallet et al., 2008b; Sadek et al., 2007). We thus targeted this crucial BG internucleus to examine the influence of dopamine depletion on the synchronization of HVS activity within and between the GP and motor cortex. Our study aimed to give important evidence for testing whether the synchronization of HVS oscillations changes in the whole cortical–BG network following dopamine loss. If confirmed, findings would make a significant contribution to understanding the functional relevance of altered synchronized HVS activity to parkinsonism.

In the present study, local-field potential (LFP) and electrocorticogram (ECoG) methodologies were employed to simultaneously record oscillations in the GP and primary/secondary motor (M1/M2) cortex areas on freely moving 6-OHDA lesioned and intact control rats. The relative powers of GP LFP and M1/M2 cortex ECoG were calculated to reveal the change in local neuronal synchrony in the GP and motor cortex. Coherences of paired LFP–ECoG and ECoG–ECoG from different recorded structures were calculated to assess the modification of inter-regional synchrony. Phase analysis between different recording regions was used to explore how dopamine depletion may influence the propagation of HVSs in the cortical–BG circuits.

2. Results

2.1. *Extent of dopamine depletion (DA depletion)*

Four weeks following unilateral injection of 6-OHDA into the medial forebrain bundle (mfb), sixteen rats were considered successfully 6-OHDA lesioned using the apomorphine rotation test. Turns could not be induced by apomorphine administration in the control rats. For the 6-OHDA lesioned rats, the number of tyrosine hydroxylase (TH) immunopositive neurons in the substantia nigra pars compacta (SNc) ipsilateral to the lesions was decreased by an average of 96.73±0.95% in comparison to the contralateral side (Fig. 1). For the control rats, the TH immunopositive neurons in the bilateral SNc did not show any difference.

2.2. *Brain state dependence and behavioral context of HVSs*

Histological detection confirmed that monopolar LFP recording electrodes were accurately located in the GP of eight rats considered successfully 6-OHDA lesioned and six control rats (Fig. 2). For both the 6-OHDA lesioned and control animals, the high-voltage spindle episodes appeared simultaneously in the M2 and M1 cortices and GP. The ECoG recorded from the M1 cortex of the 6-OHDA lesioned rats (Fig. 3) showed that HVSs occurred during two types of brain states. Most of the HVSs followed the awake state, characterized by desynchronization of ECoG and preceded another awake state (Fig. 3A). The remaining HVSs followed the awake state and preceded the sleep state (Stage I sleep) which shows "mixed activity" in ECoG recording (Fig. 3B). For all animals in both the 6-OHDA lesioned group and the control group, HVSs were found to emerge spontaneously from background brain oscillatory activity in awake rats while the animal was quietly resting, and disappeared immediately when the animals moved, as observed by continuous 24-hour video monitoring.

2.3. *Effects of DA depletion on general features of HVSs*

In the ipsilateral side of 6-OHDA lesions, HVS episodes recorded from ECoG in M2 and M1 cortices and LFP in GP, were all clearly longer in the 6-OHDA lesioned condition than that in the control condition (Fig. 4). In the control condition, the mean duration of one HVS was 1.95±0.19 s ($n=6$; Fig. 5A), while in the dopamine depletion condition, the HVSs were significantly longer ($t(12)=-11.580$, $p<0.001$), with a mean duration of 3.36±0.25 s ($n=8$; Fig. 5A). In addition, the number of HVSs in the 6-OHDA lesioned rats was significantly greater