Experimental Neurology 261 (2014) 563–577

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Functional correlates of exaggerated oscillatory activity in basal ganglia output in hemiparkinsonian rats

Elena Brazhnik, Nikolay Novikov, Alex J. McCoy, Ana V. Cruz, Judith R. Walters *

Neurophysiological Pharmacology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-3702, USA

ARTICLE INFO

Article history:
Received 2 May 2014
Revised 8 July 2014
Accepted 20 July 2014
Available online 30 July 2014

Keywords:
Parkinson's disease
Basal ganglia
Substantia nigra pars reticulata
Beta frequency
Local field potentials
Gait
Motor cortex
Dopamine
6-Hydroxydopamine
Serotonin
Oscillations

ABSTRACT

Exaggerated beta range (13–30 Hz) synchronized activity is observed in the basal ganglia of Parkinson's disease (PD) patients during implantation of deep brain stimulation electrodes and is thought to contribute to the motor symptoms of this disorder. To explore the translational potential of similar activity observed in a rat model of PD, local field potentials (LFPs) and spiking activity in basal ganglia output were characterized in rats with unilateral dopamine cell lesion during a range of behaviors. A circular treadmill was used to assess activity during walking; hemiparkinsonian rats could maintain a steady gait when oriented ipsiversive to the lesioned hemisphere, but were less effective at walking when oriented contraversive to lesion. Dramatic increases in substantia nigra pars reticulata (SNpr) LFP oscillatory activity and spike-LFP synchronization were observed within the beta/low gamma range (12–40 Hz) in the lesioned hemisphere, relative to the non-lesioned hemisphere, with the dominant frequency of spike-LFP entrainment and LFP power varying with behavioral state. At 3 weeks postlesion, the mean dominant entrainment frequency during ipsiversive treadmill walking and grooming was 34 Hz. Other behaviors were associated with lower mean entrainment frequencies: 27–28 Hz during alert non-walking and REM, 17 Hz during rest and 21 Hz during urethane anesthesia with sensory stimulation. SNpr spike-LFP entrainment frequency was stable during individual treadmill walking epochs, but increased gradually over weeks postlesion. In contrast, SNpr LFP power in the 25–40 Hz range was greatest at the initiation of each walking epoch, and decreased during walking to stabilize by 6 min at 49% of initial values. Power was further modulated in conjunction with the 1.5 s stepping rhythm. Administration of L-dopa improved contraversive treadmill walking in correlation with a reduction in SNpr 25–40 Hz LFP power and spike synchronization in the dopamine cell lesioned hemisphere. These effects were reversed by the serotonergic 1A agonist, 8-OH-DPAT. While the prominent spike-LFP phase locking observed during ongoing motor activity in the hemiparkinsonian rats occurs at frequencies intriguingly higher than in PD patients, the synchronized activity in the SNpr of this animal model has much in common with oscillatory activity recorded from the basal ganglia of the PD patients. Results support the potential of this model for providing insight into relationships between synchronization of basal ganglia output induced by loss of dopamine and motor symptoms in PD.

Published by Elsevier Inc.

Introduction

Recordings of neuronal activity from the subthalamic nucleus (STN) and internal globus pallidus (GPi) of Parkinson's disease (PD) patients during implantation of deep brain stimulation electrodes show exaggerated synchronized and oscillatory activity in the beta frequency range (13–30 Hz) (Alonso-Frech et al., 2006; Brown, 2003; Brown et al., 2001; Kuhn et al., 2005; Levy et al., 2002; Priori et al., 2004). Evidence that this beta range oscillatory activity is reduced by L-dopa treatment in the STN and GPi of PD patients (Alonso-Frech et al., 2006; Brown, 2003; Brown et al., 2001; Levy et al., 2002; Priori et al., 2004) in conjunction with improvement in motor function (Brown and Williams, 2005; Kuhn et al., 2006; Weinberger et al., 2006) has led to considerable interest in the source of this activity and its role in the development of parkinsonian symptoms.

Animal models of PD also show increases in synchronized and oscillatory activity in the basal ganglia (Avila et al., 2010; Belluscio et al., 2013; Bergman et al., 1994; Brazhnik et al., 2012; Delaville et al., 2014; Kita and Kita, 2011a; Mallet et al., 2008b; Murer et al., 2002; Raz et al., 2001; Sharott et al., 2005; Tachibana et al., 2011; Tseng et al., 2001; Walters et al., 2007). Ideally, these models should be able to provide insight into how loss of dopamine triggers such dramatic changes in basal ganglia activity and whether firing patterns in specific frequency ranges are ultimately pathological, compensatory, or simply confounding. One caveat, however, is that the peak frequencies of abnormal oscillations observed in animal models of PD show substantial variability across species and behavioral states, prompting questions about whether the increased oscillatory activity evident in animal models is translationally

* Corresponding author at: Neurophysiological Pharmacology Section, NINDS, NIH, 35 Convent Drive, Building 35 Room 1C905, Bethesda, MD 20892-3702, USA.
E-mail address: waltersj@ninds.nih.gov (J.R. Walters).

http://dx.doi.org/10.1016/j.expneurol.2014.07.010
0014-4886/Published by Elsevier Inc.

relevant to the oscillatory activity thought to be pathological in human PD. For example, in dopamine-depleted non-human primates, dominant frequencies of oscillatory spiking activity recorded from the STN and GPi are typically bimodally distributed in the 3–15 Hz range (Gatev et al., 2006; Heimer et al., 2006; Leblois et al., 2007; Raz et al., 2000; Tachibana et al., 2011), lower than the 13–30 Hz peak frequencies noted most commonly in local field potential (LFP) recordings from alert PD patients (Alonso-Frech et al., 2006; Brown, 2003; Kuhn et al., 2009; Levy et al., 2002; Priori et al., 2004; Weinberger et al., 2006). Moreover, peak frequencies of exaggerated oscillatory activity are in the 30–35 Hz range in LFP recordings from basal ganglia output nuclei in hemiparkinsonian rats during treadmill walking (Avila et al., 2010; Brazhnik et al., 2012), while studies in urethane-anesthetized hemiparkinsonian rats report synchronization in the 1 Hz range during deep anesthesia (Tseng et al., 2001; Walters et al., 2007) and in the 20 Hz range during states of global activation (Mallet et al., 2008a; Mallet et al., 2008b; Moran et al., 2011). On the other hand, recordings from PD patients also show some variability in peak frequency from patient to patient under seemingly similar recording conditions, prompting questions about whether the specific frequency at which basal ganglia output becomes synchronized is critical, or even relevant, to the nature of the motor deficits in PD patients (Kuhn et al., 2009).

The present study sought to develop a more detailed description of relationships between oscillatory activity in basal ganglia output, behavioral state, and motor dysfunction in a rodent model of PD. Our goal was to determine whether the exaggerated oscillatory activity in the basal ganglia of the hemiparkinsonian rat model appears sufficiently relevant to the oscillations observed in the PD patient be helpful in elucidating how exaggerated oscillatory activity relates to the symptomology of PD. Chronic recordings of spike and LFP activity were performed in the substantia nigra pars reticulata (SNpr) in rats with unilateral 6-hydroxydopamine (6-OHDA)-induced dopamine cell lesion. Simultaneous recordings from the SNpr in the lesioned and non-lesioned hemispheres allowed assessment of the effect of dopamine cell lesion on basal ganglia output over a range of behavioral states. Dominant frequency and power of oscillatory neural activity, spike synchronization, and firing rate in the SNpr were analyzed over different time scales in conjunction with effects of L-dopa treatment on motor symptoms.

Materials and methods

All experimental procedures were conducted in accordance with the NIH Guide for Care and Use of Laboratory Animals and approved by the NINDS Animal Care and Use Committee. Every effort was made to minimize the number of animals used and their discomfort.

Subjects and behavioral training

Male Long–Evans rats (Taconic Farm, USA), weighing 250–300 g were housed with *ad libitum* access to food and water in environmentally controlled conditions with a reversed 12:12 h light:dark cycle (lights on at 6 PM). All rats (n = 13) received unilateral dopamine cell lesions as described below. Rats with electrodes implanted bilaterally in the SNpr (n = 9) were used for lesioned hemisphere vs. non-lesioned hemisphere comparisons of LFP spectral power, spike-LFP synchronization and dominant entrainment frequency across behavioral states and for assessment of motor deficits during treadmill walking before and after administration of drugs (see below). An additional group of rats (n = 4) with the electrodes unilaterally implanted in the SNpr of the dopamine-lesioned hemisphere were used to explore the relationship between the expression of synchronized activity in the high beta/low gamma frequency range (25–40 Hz) in the SNpr and the extent of motor deficits over the course of 2 h following administration of a therapeutic dose of L-dopa. During the week before surgery, rats were handled daily and trained to walk on a circular treadmill (Avila et al., 2010). Training consisted of 3–5 daily sessions during which rats were encouraged to walk for 5–10 min in both clockwise and counterclockwise directions at variable speeds with rest periods between walking epochs. At the end of the training, the rats were able to walk steadily in both directions at the speed of 9 RPM. After unilateral dopamine cell lesion, the hemiparkinsonian rats could make reasonable progress on the circular treadmill if they were oriented in the direction ipsiversive to the hemisphere with the dopamine cell lesion, with their affected paws on the outside of the circular path. They had significant difficulty walking in the direction contraversive to the lesion with their affected paws on the inside of the circular track.

Surgical procedures

Unilateral lesion of the nigrostriatal pathway and implantation of electrodes for recording LFP and spikes and EMG electrodes were performed during the same surgery. Rats were anesthetized with 75 mg/kg ketamine (Ketaved, Vedco, St. Joseph, MO) and 0.5 mg/kg medetomidine HCl, administered i.p. (Dexdomitor, Pfizer Animal Health, New York, NY) and placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA) with heads fixed with atraumatic earbars. The incision area was shaved and a long acting local anesthetic (1%, Polocaine, APP Pharmaceuticals, LLC, Schaumberg, IL) was injected along the intended incision lines. Ophthalmic ointment (Lacrilube, Akorn, Inc., Lake Forest, IL) was applied to prevent corneal dehydration and lidocaine gel was placed in the ear canals. A heating pad was used to maintain body temperature at 37 °C. Small supplemental doses of ketamine were administered during the surgery as needed.

Unilateral lesion of the nigrostriatal pathway

Thirty minutes prior to intracerebral injections of 6-OHDA HBr (Sigma-Aldrich Co., St. Louis, MO) into the left medial forebrain bundle to destroy the dopaminergic nigrostriatal pathway, desmethylimipramine HCl (15 mg/kg, i.p.) (Sigma-Aldrich Co.) was administered to protect noradrenergic neurons. A hole was drilled in the skull at 4.4 mm anterior to the lambdoid suture, 1.2 mm lateral to sagittal suture. Six micrograms of 6-OHDA HBr in 3 μl of 0.9% saline with 0.01% ascorbic acid were infused via a 27 gauge stainless steel cannula into the medial forebrain bundle (8.3 mm ventral to the skull surface) at a rate of 1 μl/min over 3 min via a syringe pump (Harvard Apparatus, Holliston, MA, USA). The cannula was left at the target site for 3 min after the infusion was completed. The efficacy of the dopaminergic lesion was assessed using the stepping test procedure at 5–7 days after the lesion (Olsson et al., 1995; Schallert and Tillerson, 1999). Rats were included in the study if they demonstrated a strong unilateral motor deficit (number of steps made by the contralateral limb <5% of steps made by the ipsilateral limbs) after the dopamine cell lesion.

Electrode implantation

Holes were drilled in the skull over the target recording sites in the left and right hemispheres. Two electrode bundles were bilaterally implanted into the SNpr at coordinates: 3.2 mm anterior to the lambdoid suture, 2.2 mm lateral from the sagittal suture and 8.0 mm ventral from the skull surface. Bundles were secured to the skull with screws and dental cement (Ortho-Jet Liquid, Lang Dental Mfg. Co., Inc, Wheeling, IL) and ground wires from each set of electrodes were wrapped around a screw located above the cerebellum. Two electrode configurations were used for these experiments: bundles, consisting of 8 stainless steel teflon-insulated microwires plus an additional 9th wire with no insulation for ~1 mm on the recording tip serving as a local reference, and arrays, consisting of 9 stainless steel microwires arranged in a 3 × 3 matrix with 200 μm between wires with the 9th reference wire at one corner of the array for recording from the larger area in the SNpr (NB Labs, Denison, TX, USA). Electrodes had impedances of ~0.6 MΩ, measured in physiological saline at 135 Hz, 9th wires had impedances