Basal Ganglia 3 (2014) 221–227

Contents lists available at ScienceDirect

Basal Ganglia

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

Review

Oscillatory activity in basal ganglia and motor cortex in an awake behaving rodent model of Parkinson's disease

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ARTICLE INFO

Article history:
Received 25 November 2013
Received in revised form 3 December 2013
Accepted 3 December 2013
Available online 12 December 2013

Keywords:
Parkinson's disease
Basal ganglia
Substantia nigra pars reticulata
Motor cortex
Beta frequency oscillations
Dopamine

ABSTRACT

Exaggerated beta range (15–30 Hz) oscillatory activity is observed in the basal ganglia of Parkinson's disease (PD) patients during implantation of deep brain stimulation electrodes. This activity has been hypothesized to contribute to motor dysfunction in PD patients. However, it remains unclear how these oscillations develop and how motor circuits become entrained into a state of increased synchronization in this frequency range after loss of dopamine. It is also unclear whether this increase in neuronal synchronization actually plays a significant role in inducing the motor symptoms of this disorder. The hemiparkinsonian rat has emerged as a useful model for investigating relationships between loss of dopamine, increases in oscillatory activity in motor circuits and behavioral state. Chronic recordings from these animals show exaggerated activity in the high beta/low gamma range (30–35 Hz) in the dopamine cell-lesioned hemisphere. This activity is not evident when the animals are in an inattentive rest state, but it can be stably induced and monitored in the motor cortex and basal ganglia when they are engaged in an on-going activity such as treadmill walking. This review discusses data obtained from this animal model and the implications and limitations of this data for obtaining further insight into the significance of beta range activity in PD.

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1. Introduction

Functional neurosurgery has provided an opportunity to record directly from the basal ganglia in the human. This opportunity most commonly arises in patients with Parkinson's disease (PD) undergoing implantation of electrodes in the subthalamic nucleus (STN) or the globus pallidus interna (GPi) for therapeutic deep brain stimulation at high frequency (DBS) [1]. The availability of direct recordings of basal ganglia activity from PD patients has led to new ideas about mechanisms underlying motor dysfunction associated with PD. Most notably, excessive synchronization of neuronal activity in the beta (12–30 Hz) frequency range has been reported in the STN and GPi of PD patients [2–7]. This activity has been hypothesized to be responsible for the akinesia and bradykinesia characteristic of PD [8–12], and it has been suggested that DBS alleviates motor symptoms in PD, to some extent, by disrupting this overly synchronized activity [13–19].

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2210-5336/$ – see front matter. Published by Elsevier GmbH.
http://dx.doi.org/10.1016/j.baga.2013.12.001

Human studies have their limitations when it comes to examination of these hypotheses. The fact that all basal ganglia recordings are performed in patients with some type of neurological disorder does not allow a clear comparison of the normal state with the diseased state before and after treatment. In addition, it is difficult to examine the relationship between the onset and progression of exaggerated oscillatory activity and the emergence of motor symptoms in PD patients as neurosurgical intervention is reserved for specific target sites and advanced disease states.

Animal models of PD provide an opportunity to explore these issues. *In vitro* as well as *in vivo* experiments allow researchers to focus on specific mechanisms from cell to network levels. Research in PD has been facilitated by the fact that many aspects of this disorder can be modeled in rodents as well as primates. The main motor symptoms are believed to be due to the loss of dopamine neurons, a cell type which is selectively sensitive to certain neurotoxins. In the late 1960s, Ungerstedt described the use of 6-hydroxydopamine (6-OHDA) as a research tool for inducing dopamine cell death in rats [20,21] and in the 1980s 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was found to have a similar effect in primates and mice [22–29].

The availability of 6-OHDA led to the widespread use of the hemiparkinsonian rat model for biochemical as well as neurophysiological studies of the effects of dopamine cell death on basal ganglia circuitry. A relatively extensive dopamine cell lesion can be obtained by infusion of 6-OHDA into the medial forebrain bundle (MFB), where it is transported into the axons of the dopamine neurons as they travel from the substantia nigra to their terminals, most prominently in the striatum and, to a lesser extent, in other basal ganglia sites and the motor cortex. Because the dopamine neurons in the basal ganglia project unilaterally, lesioning the dopamine neurons in one hemisphere induces only indirect, presumably minor effects on the contralateral hemisphere. Since the dopamine system in one hemisphere remains intact, the animals are able to eat and move around in spite of having severe dopamine depletion in the lesioned hemisphere. The motor symptoms that emerge are mainly evident on the side of the body contralateral to the 6-OHDA lesion. This review will discuss recent studies investigating the utility of the awake, behaving hemiparkinsonian rat for obtaining insight into the relationships between motor symptoms, behavioral state and synchronized activity in basal ganglia and motor cortex in PD.

2. The treadmill walking task

A significant challenge in chronic recording studies in animal models of PD is how to control the animal's behavior so that tasks performed are relevant to PD but still capable of being expressed by both control and lesioned rats. An effective strategy has involved the use of a circular treadmill with a track just wide enough to allow a rat to walk forward without turning around (Fig. 1A) [30]. The treadmill, designed in collaboration with the National Institutes of Health's Section on Instrumentation, rotates at a relatively slow speed (1–1.5 s between steps) and the presence of a stationary paddle encourages the rat to maintain continuous locomotion. Before the 6-OHDA-induced dopamine cell lesion, rats are trained to walk in both directions on the circular treadmill. After unilateral dopamine cell lesion, the hemiparkinsonian rats retain their ability to walk steadily in the direction ipsiversive to the lesion, with their affected paws on the outside of the circular path. However, the ability of the rat to walk contraversive to the lesion, with their affected paws on the inside of the circular path, is dramatically impaired. They have considerable difficulty making steady progress, and generally freeze or rear and attempt to turn around (Fig. 1B). This arrangement allows comparisons of basal

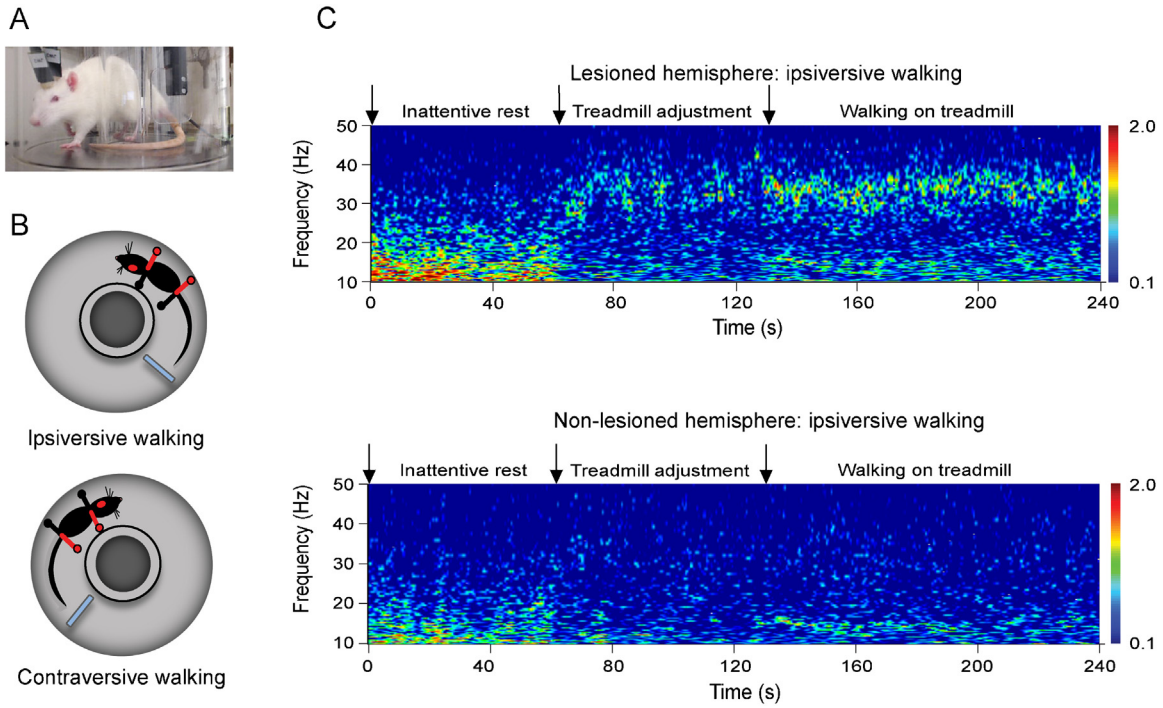

Fig. 1. Representative example of treadmill walking and SNpr LFP activity in lesioned and non-lesioned hemispheres. (A) Rat walking on the treadmill with chronically implanted electrodes. (B) Schematic representation of the rat walking ipsiversively and contraversively to the lesioned hemisphere (red dot) with the impaired paws (red) outside and inside the treadmill, respectively. (C) Wavelet based scalogram of simultaneously recorded SNpr LFP activity from the lesioned hemisphere (top) and the non-lesioned hemisphere (bottom) during one epoch of inattentive rest, treadmill adjustment and treadmill walking. During the treadmill adjustment period, low beta LFP power (12–18 Hz) was reduced in the SNpr in both intact and lesioned hemispheres compared to inattentive rest epochs. Meanwhile, SNpr LFP power increased in the 25–30 Hz range in the lesioned hemisphere. When the rats began to walk, robust 30–35 Hz high beta/low gamma range activity became quite prominent in the SNpr of the lesioned hemisphere. Data taken in part from Avila et al. [30].