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Oscillatory Activity in Basal Ganglia and Motor Cortex in an Awake Behaving Rodent Model of Parkinson's Disease

Claire Delaville, Ana V. Cruz, Alex J. McCoy, Elena Brazhnik, Irene Avila, Nikolay Novikov, and Judith R. Walters*

Neurophysiological Pharmacology Section, National Institute of Neurological Disorders and Stroke National Institutes of Health, Bethesda, MD20892-3702USA

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.

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

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*Correspondence should be addressed to Judith R. Walters, Ph.D., Neurophysiological Pharmacology Section, NINDS, NIH, 35 Convent Drive, Building 35 Room 1C905, Bethesda, MD 20892-3702 USA waltersj@ninds.nih.gov Tel: 301-496-2067.

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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].

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 1960's, 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 1980's 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.

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 sec 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 ganglia activity in the intact and lesioned hemispheres in the hemiparkinsonian rats as they walk ipsiversively on the treadmill. Similar recordings can be performed in control rats walking at the same speed. The marked difficulty the rats experience with contraversive walking provides an index of disability, as contraversive walking is notably improved by dopamine replacement with levodopa (L-DOPA) [30, 31] or dopaminergic agonists such as apomorphine. After treadmill walking epochs, rats tend to remain inactive for a period of time and often engage in inattentive rest. Thus, comparisons can be made between the rest and walk states.

Local field potential (LFP) and spike synchronization in basal ganglia output in the hemiparkinsonian rat

The first studies in the awake behaving rats using this model ([30, 31] focused on comparisons between activity in the substantia nigra pars reticulata (SNpr), the principal basal ganglia output nucleus, in the intact and dopamine cell-lesioned hemispheres (dopamine cell loss >90%, as indicated by tyrosine hydroxylase staining) during epochs of rest and treadmill walking in the ipsiversive direction. During epochs identified as inattentive rest, SNpr LFP power in the 12-18 Hz low beta range was significantly greater in the dopamine-depleted hemispheres than in control hemispheres (either contralateral to the 6-OHDA lesions in bilateral recordings or in control rats with no lesion). Also notable was the intermittent presence of prominent high voltage spindles in the LFPs recorded during inattentive rest epochs, consisting of 3-5 sec epochs, when the LFP displayed prominent oscillations at frequencies of 5-13 Hz. This phenomenon has been described as being considerably more evident in the basal ganglia and motor cortex of the 6-OHDA-lesioned rat than in the control rat [32-34]. Interestingly, we noted that when a prominent high voltage spindle was present in the SNpr of the 6-OHDA lesioned hemisphere, a much smaller version, with shorter duration and lower amplitude could regularly be found occurring simultaneously in LFP recordings from the contralateral intact SNpr. Spiking activity in the SNpr was strongly phase-locked with these spindles in the lesioned hemisphere, but less so in the intact (I. Avila, data not shown).

At the end of each rest epoch the treadmill was turned on. As the rat was alerted by the activation of the treadmill, low beta LFP power (12-18 Hz) was reduced in the SNpr in both intact and lesioned hemispheres. As the rat began to move and adjust its stepping to the speed of the treadmill, SNpr LFP power increased in the 25-40 Hz range in the lesioned hemisphere. When the rats began to walk at a constant speed in the direction ipsilateral to the lesion, 30-35 Hz high beta/low gamma activity became strikingly prominent in the SNpr

of the lesioned hemisphere. Similar activity was also evident in the dopamine-lesioned hemisphere when the rats were oriented in the opposite (contraversive) direction on the treadmill where they showed greater difficulty walking in a steady manner [30, 31]. The observations of this abnormal activity in the lesioned hemisphere during orientation in the contraversive direction, as with orientation in the ipsilateral direction, is consistent with the fact that even though the animal was having difficulty walking steadily in the contraversive direction, he was frequently rearing or moving to try to turn around, and therefore still attempting to use both the impaired and intact paws. Thus, in the hemiparkinsonian rat, dopamine loss is associated with changes in synchronization of SNpr activity in low beta or high beta/low gamma ranges in the lesioned hemisphere depending on the behavioral state of the rat.

Spike triggered waveform averages were calculated to assess the extent to which the increases in exaggerated oscillatory LFP activity were associated with increases in phase-locked spiking. During rest periods in which low beta activity was prominent, and during periods of high beta/low gamma activity when rats were walking, spikes were significantly more phase locked to the dominant frequency expressed in the LFP in the dopamine cell-lesioned hemisphere than they were to the same frequency in the intact hemisphere. Interestingly, LDOPA administration reduced the synchronization of activity observed in the lesioned hemisphere in the hemiparkinsonian rats and improved their ability to walk in the contraversive direction on the treadmill. This was consistent with the efficacy of L-DOPA in reducing exaggerated synchronization in the beta range in PD patients [30, 31].

These observations are relevant to a clinically pertinent issue regarding the increased oscillatory activity in the basal ganglia observed after loss of dopamine: the hypothesis that dysfunctional synchronization in basal ganglia, and basal ganglia output, plays a role in mediating motor symptoms in PD [8-12, 35, 36]. In the extensively lesioned hemiparkinsonian rat, the increase in synchronized spiking activity and high beta/low gamma LFP power, evident in the SNpr by 7 days post-lesion, is clearly associated with difficulties in gait and responsive to L-DOPA administration. However, a recent study has raised doubt about the relationship between increases in oscillatory activity and motor dysfunction in this animal model when dopamine cell lesion is less extensive. Quiroga-Varela and colleagues [37] recorded LFP and spike activity from the SNpr during the development of a progressive bilateral dopaminergic lesion mediated by intracerebral administration of 6-OHDA into the third ventricle over 7 days [38]. The results failed to show evidence of increases in synchronized activity in SNpr recordings during treadmill walking in spite of clear evidence of a reduction in motor function and bilateral loss of dopamine neurons of approximately 65%. Similarly, 6-OHDA MFB injections inducing a comparable partial loss of dopaminergic neurons also failed to induce increased oscillatory activity in the 30-35 Hz range in the SNpr [37]. One implication of these findings may be that relatively subtle and localized changes in neuronal synchronization and coherence in basal ganglia circuits are sufficient to provoke motor symptoms. Alternatively, it may be possible that the robust increase in synchronized activity observed in the parkinsonian rat represents a maladaptive compensatory process which emerges after substantial dopamine cell loss. It is interesting to consider that these observations in the rodent model may be relevant to reports of a lack of correlation between onset of motor symptoms and

exaggerated beta range synchronization in the basal ganglia in PD patients and primate models of PD [7, 39-41].

High beta/low gamma LFP synchronization and coherence in motor cortex and basal ganglia during rest and walk in the hemiparkinsonian rat

Another area of controversy with respect to the synchronized activity observed in the basal ganglia after loss of dopamine is the source of these oscillations. This has proven a complex problem to address, even at the level of a rodent model of PD. Early studies in the anesthetized hemiparkinsonian rat focused on the effects of dopamine cell loss on striatal sensitivity to cortical input [42]. These studies lent support to the idea that dopamine depletion facilitates the transmission of cortical rhythms through the striatum to the basal ganglia. Indeed, a number of investigators have shown that the transmission of slow wave activity from cortex to downstream nuclei is markedly enhanced by dopamine cell lesion [42-48]. While it is appealing to think that faster cortical frequencies might similarly exert an enhanced effect on striatal output after loss of dopamine, the studies by Zold and colleagues [49, 50] show that oscillations with frequencies in the 20 Hz range and higher are not efficiently transmitted through the striatum in the rat after 6-OHDA lesions. This raises questions about the potential for cortical input to the basal ganglia to contribute to the emergence of synchronized 30-35 Hz activity observed in the SNpr during treadmill walking in the hemiparkinsonian rat, and calls attention to a role for the hyperdirect pathway from the cortex to the STN [51]. In addition, *in vitro* studies and *in vivo* studies in anesthetized rats have provided evidence for emergence of oscillatory activity in the beta range in the globus pallidus externa (GPe)-STN circuit after loss of dopamine [52-57]. These studies suggest that changes in the properties of the reciprocal connectivity between STN and GPe could bring the network into a regime that intrinsically oscillates in the beta range, adding another possibility to the ways in which loss of dopamine could promote entrainment of oscillatory activity in the basal ganglia in PD.

Relevant to these considerations, we examined whether LFPs in the motor cortex in the dopamine cell-lesioned hemisphere show increases in oscillatory activity in the same 30-35 Hz frequency range during treadmill walking as observed in the SNpr [31]. And indeed, motor cortex LFP activity recorded 1-4 weeks after dopamine depletion showed marked increases in the 30-35 Hz range during treadmill walking which was highly coherent with the SNpr LFP activity in the dopamine-lesioned hemisphere. While these observations are consistent with the idea that cortical activity contributes to the entraining of oscillatory activity in the basal ganglia after loss of dopamine, it is not clear how the dominant frequency becomes focused in the 30-35 Hz range in the dopamine-lesioned hemisphere. During treadmill walking, a broad band of modest LFP power in the 40-50 Hz range is present in the control rat. There is very little activity in the 30-35 Hz range in the motor cortex LFP prior to 6-OHDA lesion [31]. Thus, the emergence of the 30-35 Hz rhythm in the SNpr is not simply a potentiation of activity normally seen in the cortex during treadmill walking.

Consistent with the above observations, LFP recordings in the GPe and STN in the hemiparkinsonian rat also showed increases in oscillatory activity in the dopamine lesioned

hemisphere, leaving open the possibility that reciprocal connections between GPe and STN could support the emergence of the high beta/low gamma oscillations. As in the motor cortex and SNpr, LFP activity in the GPe and STN nuclei was more entrained to the 30-35 Hz rhythm during treadmill walking in the dopamine cell-lesioned hemisphere relative to the control hemisphere, although, as shown in Fig 2, lesioned vs intact hemisphere ratios are greater for motor cortex and SNpr. The increase in 25-40 Hz range power in the lesioned hemisphere relative to the non-lesioned hemisphere is 2-fold in GPe and STN, 3-fold in motor cortex, and 5-fold in SNpr. Administration of L-DOPA significantly reduced the expression of LFP power in this range in all 4 areas, as seen with respect to beta range activity in the PD patients. Subsequent administration of 8-OH-DPAT, a serotonergic 5-HT1A agonist, reversed the effect of L-DOPA in the 25-40 Hz frequency range (Fig 2). This 5-HT1A agonist has been shown to reduce dopamine levels in the striatum after L-DOPA treatment [58].

The relatively larger increase in LFP power in the high beta/low gamma range during treadmill walking in the SNpr, as compared to increases in motor cortex, GPe, and STN in the hemiparkinsonian rat (Fig. 2), calls attention to the potential for the SNpr to exert downstream effects on the ventral medial (VM) thalamus, the principal target of SNpr innervation. This further suggests an additional mechanism which could contribute to increases in synchronized activity in the basal ganglia: SNpr-mediated entrainment of thalamocortical circuitry to the 30-35 Hz rhythm. To examine the possibility of entrainment of high beta/low gamma synchrony throughout the basal ganglia-thalamocortical circuit, cortical LFP waveforms were band-pass filtered between 25-40 Hz and used as a common temporal reference to establish the relationship between synchronized single cells in motor cortex and SNpr. The data showed that SNpr neurons – which were significantly phase-locked to the cortical LFP filtered in the 25-40 Hz frequency range with a 32 ms average cycle – spiked approximately 17 ms after the mean spiking of the cortical single units. Cortical neurons which were significantly phase-locked to the same cortical LFPs, in turn, fired around 15 ms after the SNpr neurons. These temporal lags are consistent with the possibility that the basal ganglia, VM thalamus, and cortical structures could be spiking in sequence to maintain the 30-35 Hz rhythm entrained within the basal gangliathalamocortical circuit. A preliminary report [59] of increased 30-35 Hz activity in the VM thalamus during treadmill walking in the hemiparkinsonian rat supports this idea. Other observations suggest that the network generating these oscillations undergoes some degree of long-term plasticity. The peak frequency of the high beta/low gamma activity seen during treadmill walking increased significantly over time, beginning at approximately 31 Hz at 7 days post-lesion and increasing about 1 Hz per week over the subsequent 3-4 weeks [31]. Together, these results suggest that another mechanism through which dopamine loss in the hemiparkinsonian rat may contribute to increased beta range synchronization is by facilitating entrainment of basal ganglia-thalamocortical network activity to a frequency compatible with the dynamic resonance of this circuit.

Implications and limitations of the hemiparkinsonian rat model

The changes in neuronal activity observed in motor circuits in the hemiparkinsonian rat, as described above, suggest that this animal model has the potential for providing insight into

PD. The fact that the rat shows increases in oscillatory activity in the basal ganglia after loss of dopamine allows investigators to study the significance of this aberrant pattern of activity and its relationship to motor dysfunction. However, it remains to be determined whether the firing patterns emerging in the rodent after loss of dopamine are sufficiently comparable to those in PD patients to allow translational insight into increased LFP synchronization and underlying mechanisms in the patient.

One concern is that the oscillations prominent in the lesioned hemisphere in the rat during treadmill walking occur at a somewhat higher frequency than the range reported for PD patients. It has been suggested that this difference could be due to the fact that oscillatory activity is not being examined during comparable behavioral states in the hemiparkinsonian rat and PD patient. Patients are not commonly engaged in motor activity as vigorous as treadmill walking while being recorded. Although motor activity is increasingly being taken into consideration in studies with PD patients [60], it is still not clear exactly how firing patterns in the basal ganglia would be affected during effort to overcome difficulties in gait.

A related concern with respect to relationships between oscillatory activity and behavioral state has to do with whether increased activity in a particular frequency range is more effective than other ranges in promoting motor symptoms in PD patients. And if so, can a rat model of PD have translational value if the motor symptoms are expressed in conjunction with exaggerated activity in a different frequency range? The 20 Hz beta range activity observed in PD patients is believed to be correlated with a state of motor preparation in normal individuals [35]. This has led to the idea that increased power in the 20 Hz frequency range may prolong or “lock in” this stage of motor preparation and thus promote akinesia or bradykinesia. One might argue that species differences could exist such that the state of motor preparation and idling is facilitated by a higher 30-35 Hz rhythm in the rat. However, recent studies by Berke and coworkers [61] suggest that increases in LFP power in the 20 Hz range in the rat are indeed associated with the same type of behaviors as in the human: action programming, rather than on-going motor activity. Increases in synchronized activity in the parkinsonian primates are also found in frequency ranges different from those observed in the PD patient. After treatment with MPTP, synchronized spiking and LFP activity in primate basal ganglia is typically reported to be in the range of 7-13 Hz [62-64]. These frequencies are lower than those commonly reported in PD patients. One conclusion that could be drawn from these differences among species is that the increase in synchronization and/or coherence of spiking activity within the basal ganglia after loss of dopamine may be more critical to motor dysfunction than the particular frequency range of the synchronization.

Conclusion

In summary, the awake, behaving hemiparkinsonian rat is a useful resource for studying relationships between motor activity and network oscillations in the dopamine-depleted brain that models advanced PD. The excessive beta range oscillations observed in the basal ganglia nuclei in hemiparkinsonian rats resemble similar neuronal activity recorded from the basal ganglia of PD patients, though differences in the dominant frequency of network oscillations are important discrepancies to consider. Opportunities for future studies in this

model include examination of the time course of the emergence of the oscillatory activity in the basal ganglia thalamocortical circuits and investigation of changes induced by this activity in specific downstream neuronal populations over time. In combination with data from *in vitro* studies, relationships between single cells and LFPs in cortical, thalamic and basal ganglia structures can illuminate mechanisms underlying the dynamic effects of loss of dopamine on motor circuits. These studies should facilitate identification of electrophysiological correlates of dysfunctional behavioral states and provide a bridge between cellular/synaptic levels and global phenomena such as oscillations, leading to insights into both normal and pathological function.

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Figure 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 lesion 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., 2010 [31]).

Figure 2. Increases in the 25-40 Hz high beta/low gamma LFP activity in the motor cortex, GPe, STN and SNpr during treadmill walking after dopamine cell lesion

A. Wavelet-based spectrogram of motor cortex LFP activity in the lesioned hemisphere during walking (left), after L-DOPA (t=0 min; 12 mg/kg combined with 15 mg/kg of benserazide, sc) and 8-OH-DPAT (t=85 min; 0.2 mg/kg, sc) injections. Note the prominent 30-35 Hz high beta/low gamma range activity during walking which is eliminated following L-DOPA treatment and was restored after 8-OHDPAT injection, a serotonergic 1A agonist known to reduce the release of dopamine via the serotonergic terminals in the striatum and reverse the behavioral and pharmacological effects of L-DOPA [65]. B. Ratios between lesioned and non-lesioned hemispheres for total power in the 25-40 Hz in motor cortex, GPe and SNpr. All structures showed significantly greater high beta/low gamma power in the lesioned compared to the non-lesioned hemisphere (ratio > 1). These increases were reduced by L-DOPA (5 mg/kg sc with 15 mg/kg benserazide, sc) and restored by 8-OH-DPAT (* p <0.05, repeated measures one-way ANOVA). C. Ratio between the lesioned hemisphere in hemiparkinsonian rats and control hemisphere in intact rats for total power in the 25-40 Hz range in STN during walking. As in the structures described in (B), STN showed significantly higher power in 25-40 Hz frequency range in the lesioned animals compared to control (ratio > 1). Also, these increases were reduced by L-DOPA (12 mg/kg combined with 15 mg/kg of benserazide, sc) and reversed by 8-OH-DPAT (# p <0.05, χ^2 test).