Slow Oscillatory Discharge in the Primate Basal Ganglia

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Wichmann, Thomas, Michele A. Kliem, and Jesus Soares. Slow oscillatory discharge in the primate basal ganglia. J Neurophysiol 87: 1145–1148, 2002; 10.1152/jn.00427.2001. Oscillations with periods in the multisecond range have previously been recorded in basal ganglia neurons of awake paralyzed rats, and in these animals were shown to be increased by systemic dopaminergic stimulation, but not altered by depletion of the nigrostriatal dopamine supply. To determine whether oscillations with frequencies below 0.5 Hz also exist in the primate basal ganglia, the spontaneous neuronal activity in the subthalamic nucleus (STN) and in the external and internal segments of the globus pallidus (GPe and GPi, respectively) was recorded with standard extracellular recording methods in two animals before and after treatment with the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Oscillations with mean periods around 80 s were identified in 30% percent of GPe neurons, 36% of STN neurons, and 48% of GPi neurons. After recording in the normal state, the animals were rendered parkinsonian by intracarotid application of MPTP. This treatment resulted in a 30% reduction of the average discharge rate in GPe, a 47% increase of the average discharge rate in STN, and a 15% increase of the average discharge rate in GPi. However, there were no changes in the proportion of cells with slow oscillatory discharge. The oscillation frequencies were slightly increased in STN but remained unchanged in GPe and GPi. The results demonstrate that multisecond oscillations commonly occur in primate basal ganglia neurons and are unchanged by treatment with MPTP. The oscillations may have roles in fundamental functions of the basal ganglia-thalamocortical network, such as the regulation of the state of arousal.

INTRODUCTION

The basal ganglia are components of several segregated larger circuits, which involve the cerebral cortex and thalamus (Alexander et al. 1986). While oscillations at frequencies above 1 Hz are a well-described phenomenon in these circuits, it has recently become clear that oscillations at much lower frequencies also occur. Thus oscillatory discharge with multisecond (15–30 s) periods were demonstrated in awake, immobilized rats in the globus pallidus, the entopeduncular nucleus, the substantia nigra pars reticulata, and the subthalamic nucleus (STN) (Ruskin et al. 1999). The frequency of these slow oscillations was increased by systemic injections of dopamine receptor agonists (Ruskin et al. 1999). The incidence or frequency of low-frequency oscillations in rodents appears not to be influenced by dopaminergic lesions (Allers et al. 2000).

We show here that similar low-frequency oscillations exist in a significant percentage of neurons in the primate basal ganglia. These oscillations appear to be unaffected by the induction of parkinsonism.

METHODS

Recording experiments

The experiments were done in two Rhesus monkeys (monkeys H and I, Macaca mulatta, 4–5 kg) in compliance with the “Principles of Laboratory Animal Care” (National Institutes of Health), and approved by the university’s Animal Care and Use Committee. Under gas anesthesia, the animals received recording chambers, stereotactically positioned to permit chronic access to STN and the external and internal pallidal segments (GPe and GPi, respectively). In subsequent recording sessions, spontaneous neuronal activity was recorded as previously described (Wichmann et al. 1999).

After recording in the normal state, the monkeys were rendered hemiparkinsonian by unilateral intracarotid injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Monkey H received two injections, 4 wk apart (total dose: 0.9 mg/kg), while monkey I received one injection (0.55 mg/kg). Both animals showed stable bradykinesia, rigidity, stooping, and flexed limb posture contralateral to the injection. Post-MPTP recording sessions started 3 mo after treatment.

Histology

At the end of the experiment, the animals were killed with pentobarbital sodium, followed by transcardial perfusion with saline and Formalin. Parasagittal sections (50 μm) were stained with cresyl violet, and recording tracks reconstructed using visible microelectrode passes and information from electrophysiological experiments concerning nuclear boundaries. To assess the degree of MPTP-induced damage to the dopaminergic system, additional sections were stained for tyrosine hydroxylase (TH).

Data analysis

Only data recorded with good quality for ≥300 s were used. The data were analyzed using the Matlab software package (MathWorks, Natick, MA). Interspike intervals, measured with a spike sorter (AlphOmega, Nazareth, Israel), were used to calculate average discharge rates and Lomb periodograms (Press et al. 1992). The discharge variability index was estimated by computing the ratio of the SD of rate estimates based on 1-s intervals and the overall average discharge rate. The highest peaks in the periodograms were used to indicate the main oscillation frequencies. In addition, scalograms (using Morlet wavelet transformation) were computed. For this, the “Time-Frequency Toolbox,” a collection of Matlab routines using time-frequency distributions for the analysis of nonstationary signals, was used (written by F. Auger, P. Flandrin, O. Lemoine, and others).

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Oscillatory frequencies ranging from 0.0067 to 0.5 Hz were analyzed. To reject transient artifacts that may result in spurious low-frequency periodogram peaks, oscillations were considered to be present only if they were detected in the periodograms ($P < 0.001$), and were also seen in raster diagrams and plots of the average discharge rate against time. Scalograms were also helpful in detecting and rejecting spectral peaks caused by brief (artifactual) events.

The data were subjected to ANOVA, and further analyses were carried out using $t$-tests for group comparisons, and $\chi^2$-tests for categorical tests. Statistical tests were carried out with the SPSS software package (SPSS, Chicago, IL).

**RESULTS**

**Behavioral state**

The animals sat quietly in a primate chair during the recording sessions. Between (but not during) recording runs they occasionally received food treats as rewards. Their state of arousal was not instrumentally measured, but they were closely observed to detect obvious drowsiness or sleep. Although only data from cells were included in this analysis in which the animals clearly remained awake throughout the recording, more subtle changes in the level of arousal cannot be excluded with the methods used here. Systematic differences in the state of arousal between the normal and the hemiparkinsonian state were not detected. To avoid oscillations in discharge due to repetitive movements or sensory input, the animals were not engaged in any form of behavioral task.

**Data sets**

Before and after MPTP, neurons were recorded from STN, GPe, and GPi throughout the entire spatial extent of the nuclei. The responses of neurons to sensory examination were not systematically tested. ANOVA did not reveal inter-animal differences in length of recording, discharge rates, incidence of oscillations, and oscillation frequencies; thus data from both animals were pooled for further analysis. The average length of recording was $571.2 \pm 97.0$ s (mean $\pm$ SD; $n = 296$ cells). In GPe, 70 cells were recorded before and 53 after MPTP; in STN, 39 cells were recorded before and 47 after MPTP; and in GPi, 46 cells were recorded before and 41 after MPTP.

**Normal state**

Throughout the recording, the animals remained awake, and neither performed any rhythmic activity nor were subjected to any rhythmic sensory inputs.

The variability of the discharge rate was considerable in many neurons. Thus a variability index $>30\%$ was detected in $52\%$ of GPe neurons, $95\%$ of STN neurons, and $26\%$ of GPi neurons.

Figure 1 shows a GPe neuron recorded in the normal state. The raster diagram (Fig. 1A) and the frequency plot (1-s bins, Fig. 1B) demonstrate that the discharge oscillates approximately every 100 s. The periodogram (Fig. 1C) shows a sharp peak at 0.0094 Hz.

Thirty percent of GPe neurons, $35.9\%$ of STN neurons and $47.8\%$ of GPi neurons showed multisecond oscillations. The average main oscillation frequency was $0.0124 \pm 0.00392$ Hz in GPe (mean period, 80.6 s), $0.0128 \pm 0.00514$ Hz in STN (mean period, 78.1 s), and $0.01236 \pm 0.00401$ Hz in GPi (mean period, 80.9 s).

**MPTP-induced parkinsonism**

ANOVA revealed significant changes in average discharge rates after MPTP. The discharge rate in GPe was lowered from $66.7 \pm 25.3$ to $46.7 \pm 19.5$ ($P < 0.001$). Discharge rates in STN and GPi increased from $24.9 \pm 8.5$ to $36.5 \pm 10.8$ ($P < 0.001$), and from $69.7 \pm 19.8$ to $80.1 \pm 20.2$ ($P < 0.05$), respectively.

After MPTP, a variability index $>30\%$ was detected in $77\%$ of GPe neurons, $77\%$ of STN neurons, and $19\%$ of GPi neurons (no significant change from the normal state). The proportion of oscillatory cells did not change with MPTP treatment (Fig. 2A). After MPTP, the oscillation frequencies were increased in STN, but unchanged in GPe and GPi (Fig. 2B). Figure 2C demonstrates that there was no difference in terms of discharge rates between oscillatory and nonoscillatory cells pre- and
post-MPTP. Regression analysis showed that there was a significant correlation between oscillation frequency and average discharge rate in STN in the parkinsonian state \( (P < 0.034) \). No correlation was found in GPe and GPi (Fig. 2D).

A quantitative analysis of the loss of dopamine was not carried out in these animals, but qualitative study of striatal TH staining revealed a near complete loss of dopamine throughout caudate and putamen on the MPTP-treated side. TH staining on the opposite side was preserved (data not shown).

**DISCUSSION**

The results demonstrate that neuronal discharge in the primate basal ganglia varies substantially over extended time periods, and that some of this variability is the result of low-frequency oscillations. With the possible exception of the STN, lesions of the dopaminergic nigrostriatal tract did not change the variability of slow oscillations. In the STN, oscillation frequencies and average discharge rates were weakly correlated. This may indicate that the MPTP-induced increase in oscillation frequencies in this nucleus may have been in part related to the significant increase in STN discharge rates in the parkinsonian state. Although already detected in a high percentage of neurons, it appears likely that the true incidence of multisecond oscillations in the basal ganglia is still higher than our estimate because of sampling limitations. In several cells with particularly long recording episodes, raster diagrams and frequency plots revealed oscillations with even longer periods than those analyzed here.

The generation of oscillatory bursts in basal ganglia discharge is better understood (e.g., Beurrier et al. 1999; Nambu and Llinas 1994; Plenz and Kitai 1999) than the slow frequency shifts described in this study. The slow oscillations described here are probably a property of the entire basal ganglia–thalamocortical network (e.g., Aladjalova 1957; Ehlers and Foote 1984; Steriade 1999; Steriade et al. 1993). Oscillations of the thalamocortical network with periods lasting up to 60 s were recently described in cats (Steriade 1999; Timofeev and Steriade 1996; Timofeev et al. 2000). This oscillatory activity may be reflected in the basal ganglia, al-

![Fig. 2. Effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment on slow oscillations in the basal ganglia. A: proportion of cells with oscillatory activity in external internal segments of the globus pallidus (GPe), subthalamic nucleus (STN), and internal segments of the globus pallidus (GPi) before (black columns) and after treatment with MPTP (gray columns). B: average oscillation frequencies of oscillating cells. C: average discharge rates of oscillatory and nonoscillatory cells before and after treatment with MPTP. The numbers at the bottom of each column indicate the number of cells recorded. D: regression analysis between oscillation frequency and average discharge rates in the basal ganglia. *P < 0.05.](http://jn.physiology.org/doi/abs/10.1152/jn.00664.2001)
though it needs to be pointed out that the thalamocortical oscillations were seen during quiet sleep, and not during wakefulness as in our animals.

The primate data are comparable to the rodent literature, except for the fact that the oscillation frequency in primates appears to be lower than that in rats, perhaps reflecting species differences. The rodent studies indicate that systemic dopamine receptor activation increases the oscillation frequency (Ruskin et al. 1999), but striatal dopamine depletion in rodents and primates does not result in overt changes in slow oscillations (Allers et al. 2000). This discrepancy could be explained by the fact that lesions of the nigrostriatal tract may have less of an effect on the dopamine supply to structures such as cortex (Lewis et al. 2001) or thalamus (Freeman et al. 2001), which may be important for the generation of slow oscillations. In contrast, striatal dopamine loss has a profound effect on high-frequency oscillations in the basal ganglia (e.g., Bergman et al. 1994; Hutchison et al. 1997; Wichmann et al. 1999).

The biological relevance of multimsec oscillations remains uncertain, although such oscillations may be linked to fluctuations in (among others) the state of arousal (e.g., Steriade 1999; Steriade et al. 1993; Terzano et al. 1985), task performance (Trimmel et al. 1990), the establishment of synaptic connectivity (reviewed by Feller 1999), slow changes in autonomic tone (Cooley et al. 1998; Kita et al. 1993), and the ability to estimate time intervals (Meck 1996). Besides their possible biological significance, slow oscillations may also impact other statistical analyses of neuronal activity. For instance, estimates of discharge rates generated from short recording records will depend on the exact time within the phase of oscillations. More accurate rate estimates may require recording from a cell across several oscillatory cycles.

REFERENCES
