



Pedunculopontine nucleus electric stimulation alleviates akinesia independently of dopaminergic mechanisms

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The symptom of Parkinson's disease that is most disabling and difficult to treat is akinesia. We have previously shown that low-frequency stimulation of the pedunculopontine nucleus can alleviate such akinesia in a macaque rendered Parkinsonian using 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine. Here, we have extended that study to show that adding stimulation of the pedunculopontine

nucleus to levodopa treatment in this Parkinsonian monkey increased its motor activity significantly more than levodopa alone. This additivity suggests that pedunculopontine nucleus stimulation may improve movement by acting at a site downstream from where levodopa therapy affects the basal ganglia. *NeuroReport* 00:000-000 © 2006 Lippincott Williams & Wilkins.

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Introduction

Akinesia is the most disabling and difficult to treat of the symptoms of Parkinson's disease. A non-dopaminergic nucleus downstream from the basal ganglia, the pedunculopontine nucleus (PPN), seems to play an important role in such akinesia. Bilateral lesions of the PPN in a primate produce irreversible akinesia [1], and also akinesia follows inhibition of the PPN by high-frequency stimulation at around 100 Hz in the normal monkey [2,3].

Giving primates 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) mimics most of the symptoms of Parkinson's disease because it destroys the pigmented cells of the substantia nigra, the same neurons that degenerate in idiopathic Parkinson's disease [4,5]. In primates treated with MPTP, akinesia may be associated with overactivity of the inhibitory projections that descend from the medial globus pallidus to the PPN [6,7], because we can partially relieve the akinesia by blocking this inhibition with the GABA antagonist bicuculline injected directly into the PPN [8]. Direct stimulation of the PPN with low-frequency electric pulses can bypass the inhibition and partially reverse akinesia in the Parkinsonian monkey [3].

Many akinetic disorders, such as late-stage Parkinsonism, multi-system atrophy, and progressive supranuclear palsy, do not respond to dopaminergic drugs, or to deep brain stimulation of the basal ganglia. Akinesia, however, is alleviated by electric stimulation of the PPN in the monkey

[3] and in humans [9,10]. As the PPN lies outside the basal ganglia and has no dopaminergic pathways, the question arises as to whether the effect of PPN electric stimulation is independent from the effects of levodopa (L-DOPA).

Method

A 16-year-old male Rhesus macaque (*Macaca mulatta*) weighing 15 kg was housed in accordance with the Home Office (UK) regulations under the Animal (Scientific Procedures) Act 1986. All procedures were performed with the prior approval of the local Ethics Committee, Oxford University and the Home Office inspectorate. Experiments on this animal to examine the effect of direct electrical stimulation of the PPN alone in the Parkinsonian macaque have previously been reported [3].

We had inserted a quadripolar custom-made deep brain electrode into the left PPN connected to a subcutaneous Itrel 3 pacemaker. The stimulator could be turned on and off, and the stimulation parameters altered remotely using an implantable pulse generator programmer (Medtronic 7432 Programmer, Minneapolis, Minnesota, USA) by placing the small transmitter head of the programmer against the subcutaneous implanted pulse generator. The animal was trained to allow us to do this in the home cage without the need for sedation, or restraint. Once we had recorded a stable baseline motor activity count for the animal and were

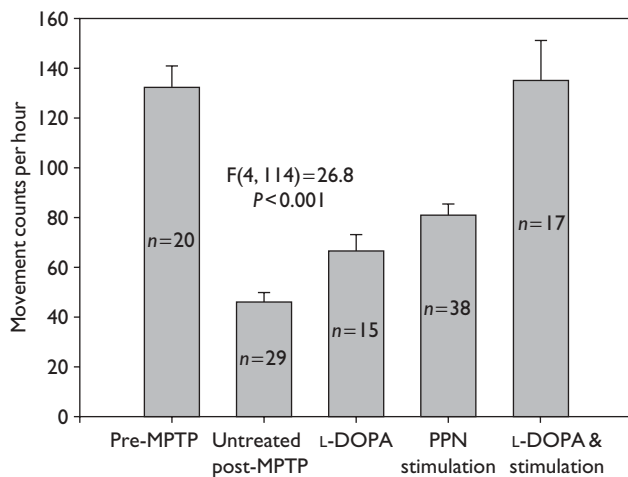


Fig. 1 Activity counts per hour before treatment with 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), after MPTP in the untreated state, with levodopa (L-DOPA) drug therapy, with pedunculopontine nucleus (PPN) stimulation and with combined L-DOPA and PPN treatment.

satisfied that the deep brain stimulator was working properly we rendered the animal Parkinsonian with 0.3 mg/kg of MPTP, slowly administered intravenously under ketamine sedation (10 mg/kg, intramuscularly 103 days after the original surgery to implant the deep brain stimulator equipment). The animal's motor activity was seen to decrease dramatically after treatment with MPTP (Fig. 1; also see Ref. [3]).

We then monitored the motor activity of the Parkinsonian macaque under four conditions: electrical stimulation of the PPN alone, L-DOPA therapy alone, a combination of L-DOPA and PPN stimulation, and neither stimulation nor L-DOPA (untreated). The L-DOPA was administered orally as Madopar, in the usual human dosage of 12.5 mg Madopar/kg. So the animal was given 187.5 mg: 150 mg L-DOPA + 37.5 mg benserazide. The combination of L-DOPA and PPN stimulation was tested by giving the same dose of Madopar and then turning on the stimulator at a frequency of 5 Hz, an amplitude of 4 V, and a pulse width of 120 μ s, stimulation parameters that produce an increase in motor activity [3].

Motor activity was recorded using a counter that triggered each time the animal crossed infrared beams passing across the cage. The counter was started between 08:00 and 12:00 h and stopped 6 h later. Just one condition was tested each day. To ensure that the animal was not showing a slow spontaneous recovery after MPTP treatment, the animal's movements were recorded without any treatment at least 1 day a week for a 6-h period, that is, without any drug treatment and with the stimulator switched off. At least 24 h separated a dose of L-DOPA and a subsequent day's recording.

Results

MPTP treatment in this monkey caused its mean movements per hour to decrease from 132 to 46 movements per hour (Fig. 1). Stimulating the PPN then increased movement count to a mean of 81 counts per hour. This increase was statistically significant (multiple comparison Tukey honest significant difference test, $P < 0.01$). By itself, L-DOPA

treatment also increased the animal's movements from 46 to 66 counts per hour, but this increase was not statistically significant ($P = 0.367$). Combining L-DOPA and PPN stimulation further increased the monkey's movements to 135 counts per hour, which was not significantly different to the level of motor activity before the MPTP administration ($P = 0.999$). Thus, the combined treatment helped return the monkey's movements to normal pre-MPTP levels.

Discussion

These results suggest that L-DOPA alone is effective in alleviating akinesia in the Parkinsonian primate, low-frequency stimulation of the PPN is a somewhat more effective treatment and that the two treatments together are not competitive but additive. This is probably because the PPN, receiving descending output from the globus pallidus, lies downstream from the basal ganglia in the locomotor circuit so that its stimulation affects locomotion more directly. Therefore, when stimulation of the PPN was combined with L-DOPA therapy, the activity counts per hour were much higher than those for either of the treatment alone, that is, the two effects were additive. Thus, PPN stimulation and L-DOPA may have independent effects on movement and at least part of the effect of stimulating the PPN may be via a non-dopaminergic pathway.

A therapy that offers symptomatic relief via a pathway not mediated by dopamine implies the possibility that akinetic symptoms that are resistant to L-DOPA, such as gait ignition failure and gait freezing, which often become particularly debilitating in the later stages of Parkinson's disease, could be alleviated by low-frequency stimulation of the PPN. In addition, it could be a successful treatment for patients suffering from akinesia caused by syndromes such as progressive supranuclear palsy and multi-system atrophy, which are also resistant to all current medical therapies.

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