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Lack of depotentiation at basal ganglia output neurons in PD patients with levodopa-induced dyskinesia

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ABSTRACT

Parkinson's disease (PD), characterized by the loss of dopaminergic nigrostriatal projections, is a debilitating neurodegenerative disease which produces bradykinesia, rigidity, tremor and postural instability. The dopamine precursor levodopa (L-Dopa) is the most effective treatment for the amelioration of PD signs and symptoms, but long-term administration can lead to disabling motor fluctuations and L-Dopa-induced dyskinesias. In animal models of PD, a form of plasticity called depotentiation, or the reversal of previous potentiation, is selectively lost after the development of dyskinetic movements following L-Dopa treatment. We investigated whether low frequency stimulation (LFS) in the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr) could induce depotentiation at synapses that had already undergone high frequency stimulation (HFS)-induced potentiation. To do so, we measured the field potentials (fEPs) evoked by stimulation from a nearby microelectrode in 28 patients undergoing implantation of deep brain stimulating (DBS) electrodes in the subthalamic nucleus (STN) or GPi. We found that GPi and SNr synapses in patients with less severe dyskinesia underwent greater depotentiation following LFS than in patients with more severe dyskinesia. This demonstration of impaired depotentiation in basal ganglia output nuclei in PD patients with dyskinesia is an important validation of animal models of levodopa-induced dyskinesia. The ability of a synapse to reverse previous potentiation may be crucial to the normal function of the BG, perhaps by preventing saturation of the storage capacity required in motor learning and optimal motor function. Loss of this ability at the output nuclei may underlie, or contribute to the cellular basis of dyskinetic movements.

Introduction

PD is a movement disorder characterized by the degeneration of dopamine neurons in the substantia nigra pars compacta (SNc). The SNc supplies dopamine to the basal ganglia, a group of nuclei involved in the control and regulation of volitional movements. When the dopaminergic input is lost, patients present with symptoms of akinesia/bradykinesia, rigidity and resting tremor. The dopamine precursor L-Dopa effectively treats these motor symptoms, but many patients become resistant to the treatment and/or develop debilitating levodopa-induced dyskinesias (LID) over time.

Experimental animal models of PD have characterized a multitude of changes in synaptic plasticity at the corticostriatal synapse, the primary input to the basal ganglia. Corticostriatal long term depression (LTD) is lost following dopamine denervation both in 6-OHDA rats (Calabresi et al., 1992) and MPTP-treated monkeys (Quik et al., 2006) due to the lack of dopamine receptor activation during the induction phase of this form of synaptic plasticity (Picconi et al., 2012). Furthermore, corticostriatal long term potentiation (LTP) is also lost following dopamine denervation in 6-OHDA rats (Picconi et al., 2003). Chronic L-Dopa treatment of 6-OHDA rats, at a therapeutic dosage similar to that used in PD patients, induces a dyskinetic response in some rats, and restores LTP in both dyskinetic and non-dyskinetic rats (Picconi et al., 2003, 2008). However, in corticostriatal slices of animals that do not develop dyskinesia, depotentiation reverses LTP at corticostriatal synapses following LFS, whereas slices from dyskinetic rats show no capacity for depotentiation (Picconi et al., 2003, 2008). The presumed consequence of this lack of depotentiation at corticostriatal synapses is that in the dyskinetic state, corticostriatal synapses that have been potentiated in vivo by a previous burst of firing would continue to show an augmented response to cortical input, irrespective of their salience for the animal's ongoing behavior.

Studies assessing basal ganglia synaptic plasticity are typically conducted at the corticostriatal synapse, but increasingly it is thought that activity-dependent synaptic plasticity occurs throughout the basal ganglia and that this form of plasticity underlies the acquisition, maintenance, and elimination of certain types of learning, including

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positive reinforcement, stimulus-reward association, and motor learning (Wickens et al., 2003). A unique characteristic of synaptic plasticity in the basal ganglia is that a certain level of endogenous dopamine and dopamine receptor activation seems to be required for its induction and maintenance. As to be expected then, disease progression in PD and the associated degeneration of the dopaminergic SNc leads to drastic alterations in basal ganglia synaptic plasticity. We have previously reported that in PD patients undergoing implantation of DBS electrodes in the STN, changes in synaptic plasticity in the ON and OFF dopaminergic medication state in the SNr, one of the primary basal ganglia output nuclei, mirrored changes described in corticostriatal slice work of the 6-OHDA model. In the absence of dopaminergic medication, LTP-like plasticity was found to be absent in the SNr following HFS, whereas following application of L-Dopa, HFS potentiated activity-dependent synaptic plasticity in the SNr (Prescott et al., 2009). A review article of that work suggested that the results opened the way to a new experimental approach in the field of PD research, strengthening the view of PD as a 'synaptopathy' that leads to neuronal network destabilization and can be rapidly counteracted by the manipulation of a neurotransmitter system (Calabresi et al., 2009). The review authors' hope was that, in the future, the study of human synaptic plasticity might shed light on the complex mechanisms underlying symptoms of the disease and the disabling long-term side effects of treatment with levodopa.

Here, we further explore alterations in human synaptic plasticity in basal ganglia output nuclei with a focus on depotentiation in patients who develop levodopa-induced dyskinesia. In order to maintain neuronal network and synaptic stability the mechanisms underlying synaptic plasticity need to be tightly controlled and, in experimental models of the PD, one critical form of synaptic plasticity, depotentiation, is selectively lost during dyskinesias. We investigated the effects of LFS on synapses in the GPi and SNr that had already undergone HFS-mediated potentiation and found that the plasticity abnormalities observed in experimental models of L-Dopa-induced dyskinesia also appear to be present in basal ganglia output neurons of PD patients with dyskinesia. That is, GPi and SNr synapses in patients with less severe dyskinesia underwent greater depotentiation following LFS than patients with more severe dyskinesia.

Methods

Patients

To examine the relationship between dopamine, depotentiation and dyskinesia in the basal ganglia output nuclei of PD patients, experiments were performed during bilateral STN or GPi DBS procedures, with the first hemisphere typically performed following 12 h of dopaminergic medication withdrawal, and where possible, the second hemisphere 20–30 min after 100–200 mg L-Dopa/carbidopa. 24 patients underwent STN DBS, 3 patients underwent GPi DBS and 1 patient underwent a bilateral pallidotomy, all for PD. All experiments were performed while the patients were awake with local anesthesia only. Patients' clinical information is shown in Table 1. The group was comprised of 22 men and 6 women and had a mean age and disease duration of 59.8 +/− 7.2 and 13.1 +/− 4.6, respectively. All experiments were approved by the University Health Network and University of Toronto Research Ethics Boards. Patients provided written informed consent prior to the procedure.

Surgical procedure & microelectrode recordings

A Leksell stereotactic frame (Elekta Inc., Atlanta, GA), was affixed to the patient's head after injection of local anesthetic. Pre-operative MR images were obtained and axial images were used to determine the x-, y- and z co-ordinates of the anterior and posterior commissures with respect to the stereotactic frame. In procedures targeting the STN, the pre-operative target was chosen to be the ventral border of STN. Coordinates of the tentative target were approximately 12 mm lateral to the midline, 2 to 4 mm posterior to the mid-commissural point and 3 mm below the AC-PC line (Hutchison and Lozano, 2000). In procedures targeting the GPi, the preoperative target was chosen to be the ventral border of GPi. Coordinates of the tentative GPi target were approximately 21 mm lateral to the midline, 3–6 mm below the AC-PC line and 1–2 mm anterior to the midcommissural point (Hutchison and Lozano, 2000).

Extracellular recordings were made with dual independently driven microelectrodes (25 μm tip length, axes 600–800 μm apart, 0.2–0.4 MΩ impedance at 1000 Hz) during the electrophysiological mapping procedure used to obtain physiological data for localizing the target for DBS quadripolar electrodes (Levy et al., 2007). Single unit activity recorded from the microelectrodes was amplified, high-pass filtered (300 Hz), and monitored on a loudspeaker and oscilloscope. Additionally, recordings were amplified 5000 times and filtered at 10 to 5000 Hz (analog Butterworth filters: high-pass, one pole; low-pass, two poles) and displayed using the two separate GS3000 amplifiers. Microelectrode data were sampled and digitized at 12 kHz with a CED 1401 (Cambridge Electronic Design [CED], Cambridge, UK).

Recording sites in GPi were localized on the basis of physiological landmarks. Irregularly firing neurons in the 60–90 Hz range were identified, along with border cells at the margins of the nucleus. The optic tract was identified by microstimulation-induced phosphenes below the ventral border of the nucleus and muscle contractions at sites posterior to the nucleus. The ventral border of STN and dorsal border of SNr were delimited by a region with sparse neuronal activity and a reduced background noise compared to that observed within the STN and SNr. The dorsal border of SNr was identified by the presence of neurons firing at a high rate (60–90 Hz) and a regular discharge pattern. The GPi and SNr were further identified by their inhibitory responses to microstimulation through the recording electrode at low intensities (thresholds of 2–4 μA) (Dostrovsky et al., 2000; Lafreniere-Roula et al., 2009).

Field-evoked potentials (fEPs) were recorded from one electrode in the SNr or GPi while stimulating with single pulses (100 μA, 0.3 ms biphasic pulse width) from a second electrode separated by 600–800 μm in the same structure, as described previously (Prescott et al., 2009). The ability of LFS (delivered to the recording electrode — see below) to depotentiate previous HFS-mediated potentiation was tested in the SNr of 13 patients at 17 sites in the OFF medication state and 14 patients at 18 sites in the ON medication state. LFS was tested in the GPi of 2 patients at 3 sites in the OFF medication state and 2 patients at 3 sites in the ON medication state. 12 patients were tested in both the OFF and ON L-Dopa states, while 1 and 2 patients were tested in the OFF and ON state only, respectively.

After obtaining a stable baseline of fEP amplitudes at 1 Hz, HFS was delivered, consisting of 4 trains of 2 s at 100 Hz, with each train separated by 10 s. Following HFS, blocks of 10 pulses at 1 Hz were tested every 30 s for 3 blocks to measure the extent of potentiation of fEP amplitudes. Next, LFS was delivered at 2 Hz for 60 s at 20 μa through the proximal electrode (the electrode used for recording the fEPs). This LFS protocol was based on a paradigm previously shown to depotentiate HFS-mediated potentiation at the corticostriatal synapse in normal rats and 6-OHDA rats receiving levodopa (Picconi et al., 2003, 2008) and also validated in earlier experiments. Blocks of 5 pulses at 1 Hz were delivered (to the stimulation electrode) at 20 and 40 s during the 60 second LFS, in order to obtain the mean fEP amplitude, followed by a block of 10 pulses at 1 Hz given immediately after the LFS train. A final block of 10 test pulses at 1 Hz was given 30 s later. The HFS protocol was then repeated followed by a block of 10 1 Hz test pulses to measure any additional changes in fEP response following LFS compared to the initial HFS (Fig. 1A).

Several trials were performed using a baseline stimulation rate of approximately 0.25 Hz to confirm the validity of 1 Hz stimulation as a valid baseline measure of synaptic strength. In these trials, test pulses