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Reduced paired pulse depression in the basal ganglia of dystonia patients

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ABSTRACT

Decreased inhibition and aberrant plasticity are key features in the pathophysiology of dystonia. Impaired short interval cortical inhibition and resultant increased excitability have been described for various forms of dystonia using paired pulse methods with transcranial magnetic stimulation of motor cortex. It is hypothesized that, in addition to cortical abnormalities, impairments in basal ganglia function may lead to dystonia but a deficit of inhibition within the basal ganglia has not been demonstrated to date. To examine the possibility that impaired inhibition and synaptic plasticity within the basal ganglia play a role in dystonia, the present study used a pair of microelectrodes to test paired pulse inhibition in the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr) of dystonia and PD patients undergoing implantation of deep brain stimulating (DBS) electrodes. We found that there was less paired pulse depression of local field evoked potentials in the basal ganglia output nuclei of dystonia patients compared with Parkinson's disease patients on dopaminergic medication. Paired pulse depression could be restored following focal high frequency stimulation (HFS). These findings suggest that abnormalities exist in synaptic function of striatopallidal and/or striatonigral terminals in dystonia patients and that these abnormalities may contribute to the pathophysiology of dystonia, either independent of, or in addition to the increased excitability and plasticity observed in cortical areas in dystonia patients. These findings also suggest that HFS is capable of enhancing striatopallidal and striatonigral GABA release in basal ganglia output nuclei, indicating a possible mechanism for the therapeutic benefits of DBS in the GPi of dystonia patients.

Introduction

Dystonia is a movement disorder characterized by involuntary muscle contractions resulting in spasms and abnormal postures. Dystonia can manifest focally, affecting an isolated body part such as the neck (cervical dystonia), or generalized to affect the whole body. Medical therapy for dystonia involves anticholinergics and GABA-B agonists such as baclofen, but many side effects limit their therapeutic efficacy. The primary treatment for focal dystonia is botulinum toxin, but the muscle paralysis lasts only a few months and patients can develop antibodies that neutralize its efficacy. Bilateral deep brain stimulation (DBS) of the globus pallidus internal segment (GPi) has proven efficacious in medically refractory cervical (Hung et al., 2007), segmental and generalized dystonia (Krauss, 2010; Ostrem and Starr, 2008), but its mechanism of action is poorly understood.

The pathophysiology of dystonia appears to be associated with abnormal plasticity and reduced inhibition at cortical, brainstem, and spinal levels. Converging evidence from animal (Martella et al., 2009; Napolitano et al., 2010) and human studies (Chen and Udupa, 2009; Quartarone et al., 2006) suggests that a key element in the pathophysiology of dystonia is impaired synaptic function leading to abnormal plasticity and motor dysfunction (for review see (Peterson et al., 2010).

Most experimental evidence of abnormal plasticity in dystonia comes from measures of sensorimotor cortical organization and physiology. However, basal ganglia dysfunction has long been implicated in dystonia, and its primary output structure, the GPi, remains the most common target for ablative and DBS treatment of dystonia. As such, abnormal plasticity in reflexes and cortical areas may be modulated by, or even secondary to abnormal plasticity in the basal ganglia, but experimentally investigating plasticity has remained difficult in basal ganglia structures. With this is mind, a model of dystonia has emerged in which a fundamental deficit within the basal ganglia generates impaired inhibition in motor cortex that results in increased excitability, abnormal processing of sensory feedback and increased striatal, brainstem, and cortical plasticity. The result is a maladaptive neural reorganization of motor circuits (Quartarone and Pisani, 2011).

Impaired short interval cortical inhibition and increased excitability have been described for various forms of dystonia using paired pulse methods with transcranial magnetic stimulation (TMS) of motor cortex. For example, pairing an initial subthreshold pulse with a suprathreshold TMS pulse at different intervals (1–15 ms) induced less inhibition in both hemispheres compared with controls (Ridding et al., 1995). A similar result was obtained using paired

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suprathreshold TMS pulses (110%, 20–200 ms intervals) and measuring surface EMG in the affected limb (Chen et al., 1997). Intracortical inhibition was reduced at all intervals below 100 ms in dystonia patients in the hemisphere contralateral to an isometric contraction of the affected limb. The origin of this cortical impairment is unknown but may share a common pathology with the basal ganglia. The internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr) are the major output nuclei of the basal ganglia. They project to thalamus and brainstem where they produce inhibition by releasing GABA (Parent and Hazrati, 1995a, 1995b). Their main inputs are also GABAergic, originating in the striatum and the external segment of the globus pallidus (GPe); they also receive an excitatory glutamatergic input from the STN (Parent and Hazrati, 1995a, 1995b). Previous studies have shown that stimulating within the GPi and SNr preferentially activates the GABAergic axon terminals of striatal and/or external pallidal neurons, thereby causing the release of GABA and inhibition of the firing of GPi and SNr neurons (Dostrovsky et al., 2000; Lafreniere-Roula et al., 2009; Prescott et al., 2009).

To gain a better understanding of the mechanism of dysfunction of basal ganglia output neurons in dystonia we assessed putative GABAergic synaptic transmission in the basal ganglia output nuclei of dystonia patients and Parkinson's disease patients on dopaminergic medication undergoing implantation of deep brain stimulating (DBS) electrodes. Short term plasticity and synaptic function were assessed in the GPi and SNr using a paired-pulse protocol by stimulating through one electrode and recording the evoked response from the other electrode. A significant factor in regulating the activity of basal ganglia output neurons is the extent of presynaptic neurotransmitter release at the striatopallidal and striatonigral synapses which can be monitored using measurements of paired pulse facilitation and depression (de Jesus et al., 2011; Dobrunz and Stevens, 1997; Warre et al., 2011). Short term plasticity involves the facilitation or depression of synaptic responses dependent on preceding activity, and therefore can modify the ability of a synapse to provide sustained inhibition or excitation. Facilitating synapses generally display high paired pulse ratios (PPR) and exhibit a low probability of neurotransmitter release whereas non facilitating synapses display lower PPRs indicative of a higher probability of release (Zucker, 1989; Zucker and Regehr, 2002).

Here, we show that basal ganglia output nuclei of dystonia patients undergo less paired pulse depression compared to Parkinson's disease patients on dopaminergic medication, suggesting altered inhibitory neurotransmitter release in dystonia patients. Interestingly, following high frequency stimulation (HFS), the paired pulse ratios in dystonia patients return to levels seen in PD patients on medication, suggesting that microelectrode HFS, and perhaps also therapeutic DBS, are capable of enhancing striatopallidal and striatonigral GABA release to normalize basal ganglia output.

Methods

Patients

Experiments were performed during stereotactic functional surgery for implantation of DBS electrodes in the subthalamic nucleus or GPi of Parkinson's disease and dystonia patients. Recording and stimulation was performed in the GPi of 5 dystonia patients (9 sites), the SNr of 2 dystonia patients (3 sites), the SNr of 8 PD patients (9 sites), and the GPi of 5 PD patients (10 sites). The clinical characteristics of the dystonia patients and Parkinson's disease patients can be found in Table 1 and Table 2 respectively. All experiments were performed while the patients were awake and under local anesthesia only. All PD patients were tested while on dopaminergic medication approximately 30 min after oral administration of 100 mg of levodopa (100/25®), except in one case where measurements were taken in the off and on dopaminergic medication states. The 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

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 (Medtronic Model 3387, Minneapolis, MN). 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 two separate Guideline System GS3000 amplifiers (Axon Instruments, Union City, CA). Microelectrode data were sampled and digitized at 12 kHz with a CED 1401 (Cambridge Electronic Design [CED], Cambridge, UK) and EMG of ipsi- and contralateral wrist flexors and extensors was sampled at 500 Hz to monitor any response to passive or active wrist movements.

Recordings from GPi and SNr

Pre-surgery, the tentative STN or GPi target was identified by brain imaging (MRI) on the basis of the stereotactic coordinates and direct imaging of the structures. Coordinates of the tentative STN target were 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). Coordinates of the tentative GPi target were 20 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). Recordings started 10–15 mm above tentative targets. Target nuclei were then localized via characteristic neuronal discharge patterns described elsewhere in detail (Hutchison et al., 1994, 1998; Lozano et al., 1995). Briefly, for nigral trajectories, after passing through thalamus and STN, the SNr was identified by the presence of neurons with a significantly higher discharge rate and more regular firing pattern (vs. STN). The dorsal and ventral borders of the STN were identified by characteristic irregular neuronal firing in 25 to 45 Hz range, often with beta rhythmic activity (15–25 Hz). The ventral border of the STN and dorsal border of the 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 SNr was identified by the presence of neurons firing at a high rate (60–90 Hz) and a regular discharge pattern. For pallidal trajectories, recording sites were localized to the GPi 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 GPi and SNr were further identified by their inhibitory responses to microstimulation through the recording electrode at low intensities (thresholds of 2–4 uA) (Dostrovsky et al., 2000; Lafreniere-Roula et al., 2009).

Stimulation protocols

Evoked field potentials (fEPs) were recorded from one electrode while stimulating with single pulses (100 uA, 0.3 ms biphasic pulse width) from a second electrode at the same dorsoventral level but separated by 600–800 μm, as described elsewhere in detail (Prescott et al., 2009). Paired pulse studies were conducted in 20 patients at 31 sites using a customized Spike2 script deployed to run a randomized set of inter-stimulus intervals (ISIs: 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300 ms, each interval repeated 3 times) at 100 uA and 0.3 ms biphasic pulse width both pre and post high frequency stimulation (HFS — 4 trains of 2 s at 100Hz, with each train