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LACK OF NON-VOLUNTARY STEPPING RESPONSES IN PARKINSON'S DISEASE

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Abstract—The majority of research and therapeutic actions in Parkinson's disease (PD) focus on the encephalic areas, however, the potential involvement of the spinal cord in its genesis has received little attention. Here we examined spinal locomotor circuitry activation in patients with PD using various types of central and peripheral tonic stimulation and compared results to those of age-matched controls. Subjects lay on their sides with both legs suspended, allowing low-friction horizontal rotation of the limb joints. Air-stepping can be used as a unique and important model for investigating human rhythmogenesis since its manifestation is largely facilitated by the absence of external resistance. In contrast to the frequent occurrence of non-voluntary stepping responses in healthy subjects, both peripheral (muscle vibration) and central (Jendrassik maneuver, mental task, Kohnstamm phenomenon) tonic influences had little if any effect on rhythmic leg responses in PD. On the other hand, a remarkable feature of voluntary air-stepping movements in patients was a significantly higher frequency of leg oscillations than in age-matched controls. A lack of non-voluntary stepping responses was also observed after dopaminergic treatment despite the presence of prominent shortening reactions (SRs) to passive movements. We argue that the state and the rhythmogenesis capacity of the spinal circuitry are impaired in patients with PD. In particular, the results suggest impaired central pattern generator (CPG) access by sensory and central activations.

Key words: Parkinson's disease, central pattern generator, muscle tone, spinal cord, shortening reaction, locomotion.

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Abbreviations: BF, biceps femoris; CPG, central pattern generator; EMG, electromyography; LG, lateral gastrocnemius; PD, Parkinson's disease; RF, rectus femoris; SD, standard deviation; SR, shortening reaction; TA, tibialis anterior; UPDRS, unified Parkinson's disease rating scale.

INTRODUCTION

Gait disturbances are frequent in advanced Parkinson's disease (PD) and are occasionally seen early in the course of the disease. They are characterized by postural changes, slow walking, festination, freezing of gait, loss of normal axial synergies and impaired arm–leg coordination (Giladi, 2001; Wright et al., 2007; Crenna et al., 2008). Patients may experience increased muscle tone in the body and neck, accompanied with difficulty when turning in bed (for example, patients may fall asleep and wake up on the same side). These patients also experience difficulty in changing the direction of walking, initiation of movement, etc., accompanied by an interesting phenomenon of freezing of gait. It is now largely accepted that the neural circuitry controlling locomotion in mammals involves a central pattern generator (CPG) (Grillner, 1981). CPG functioning depends on peripheral sensory feedback, supraspinal inputs and the presence of modulators Shik, 1983; Orlovsky et al., 1999; Pearson, 2004; Ivanenko et al., 2006a, 2009; Jordan et al., 2008). To what extent are gait disturbances in PD a result of impaired feedback, compromised supraspinal control or the rhythmogenesis capacity of spinal CPGs?

There are somewhat contradictory data on the rhythmogenesis capacity in PD. On the one hand, patients walk slowly with short steps. On the other hand, a paradoxical kinesis is often observed – spontaneous propulsion in response to asymmetrical load, e.g., brisk acceleration backward, forward or even sideways in response to grasping the load by the hand. Thus, the CPG activity may be in different states. Furthermore, there are normally certain phase relationships between arm and leg movements during walking, while the typical symptom in PD is a lack of arm movements, suggesting an impaired linkage between cervical and lumbosacral pattern generators. However, it is also known that patients with PD can easily ride a bike (Snijders et al., 2011). Thus, the CPGs may work, but something is absent or interferes with normal functioning of neuronal structures when walking.

Under normal conditions, it is difficult to investigate impairments in the CPG functioning due to interference with the ongoing task of body weight and balance control (including intense feedback). Therefore, our aim was to examine the CPG function in conditions not-complicated by these two factors. To this end, we used a previously developed approach for evoking

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air-stepping movements in a gravity neutral position in the absence of foot-support interactions. Indeed, air-stepping can be used as a unique and important model for investigating human rhythmogenesis since its manifestation is largely facilitated by the absence of external resistance (Gurfinkel et al., 1998; Selionov et al., 2009; Gerasimenko et al., 2010). We applied various central and sensory tonic stimuli previously shown to be effective in eliciting automatic air-stepping in healthy humans, we also recorded voluntary stepping and leg muscle tone at rest. The presence of rhythmic stepping responses and their relation to disease progression as measured by unified Parkinson's disease rating scale (UPDRS) and the effect of anti-Parkinsonian medication was assessed in 25 PD compared to age-matched controls. The results are discussed in the context of impaired muscle tone and rhythmogenesis in PD.

EXPERIMENTAL PROCEDURES

Subjects

A total of 47 subjects participated in this study. Twenty-five subjects (60.2 ± 8.9 year, range 41–77 year, 18 male, 7 female) had PD and were undergoing dopaminergic treatment (Table 1). Twenty-two subjects were healthy age-matched controls (57.4 ± 10.0 year, 13 male, 9 female). The average disease duration was 4.1 ± 3.1 year (range 0.3–10 year). Level of disability was evaluated using the Hoehn–Yahr scale. Only mild to moderate affected patients were included in this study, showing a Hoehn–Yahr level varying from 1 to 3 (Table 1). All subjects provided informed consent in accordance with the local ethical committee regulations for human subjects' studies and the Helsinki declaration.

The Parkinson's subjects were tested in the morning after abstaining from anti-Parkinsonian medication overnight (21 patients); the wash-out period was at least 12 h in the OFF-medication state. Four patients (Hoehn–Yahr level 3) came to the lab and were recorded first in the ON-medication state. They were recorded again several hours later in OFF. Subjects OFF-medication was assessed with the UPDRS score prior to participating in the experimental protocol. All subjects were able to stand and walk for periods of ⩾30 min without rest. After the subjects completed the OFF-medication portion of the protocol, they took their normal morning dosage of medications. About 1 h after taking their medication, the UPDRS motor score was obtained again and the protocol was then repeated ON-medication. The UPDRS scores decreased for all PD subjects when ON-medication (20.2 ± 6.0 SD) compared to when OFF-medication (22.6 ± 6.6 SD) (paired 2-tailed *t*-test; $p < 0.01$).

Protocol

The total duration of the ON- and OFF-medication sessions was about 2 h each. Four experimental conditions were investigated.

I. Overground walking: Patients were asked to walk at a natural self-selected speed along a 20-m walkway in the corridor (30 m long, 4 m in width, 4 m in height).

II. Voluntary air-stepping: The subjects were asked to produce voluntary air-stepping movements at a natural cadence while lying in the gravity neutral position. The experimental setup (Fig. 1A) was similar to that described in detail in previous studies (Gurfinkel et al., 1998; Selionov et al., 2009). To avoid the effects of gravity and external resistance, the subjects lay on their sides with the upper and lower legs suspended to permit their unimpeded motion in the horizontal plane (Fig. 1A). Both legs were supported using long ropes attached to the ceiling (height, 4 m) so that they provided low-friction pendulum-like leg motion with a limited vertical motion component. The shank segment of the right (lower) limb was placed on a 2.5-m long horizontal wooden board that was suspended from the ceiling using two vertical ropes of 3-m length. The horizontal board did not interfere with the motion of the upper leg. A bearing junction was introduced between the shank and the board, allowing free rotation of the shank relative to the stick around the vertical axis. The left limb was suspended directly from the ceiling using a long rope attached to the shank segment (Fig. 1A). The weight of the upper- and lower-limb suspension systems (0.9 and 1.5 kg, respectively) was much less than that of the limb so that it had minimal impact on the inertia of the system.

III. Responses to passive movements in the ankle, knee and hip joints: Rigidity was quantified by the amount of torque required to change joint position during externally imposed movement. The subjects lay on their sides with the upper and lower legs suspended (as in the protocol II). When lying down, each subject's relaxed, suspended leg assumed the equilibrium position with joint angles determined by the relative passive stiffness of agonist and antagonists and other soft tissues around the joints. The hip angle in the initial position varied between 135° and 160° and the knee angle between 115° and 155° (180° refers to the hip and knee angles of the extended leg with the thigh and shank segments being parallel to the trunk). The experimenter maintained a more proximal leg segment stationary by one hand while slowly changing joint position by applying a horizontal force (measured by strain gauge sensors) by another hand to a more distal segment (Fig. 1B). The movement was imposed slowly (ramp and hold angular motion profile, Fig. 2) and after a few seconds the experimenter slowly released the distal segment so that it could return to its initial position. The advantage of manual release was also that it allowed a measure of any failure to return to the initial position and thus the degree of plasticity in response to passive mechanical perturbation (Fig. 2, see also Results). A similar procedure was used for all three leg joints, the angular excursion being ~20° (except for ankle plantar flexion: ~10–15°). Larger plantar flexion angles were difficult to apply in our experimental conditions since they required considerably larger efforts due to a highly non-linear force–displacement relationship in the passive ankle joint (Gottlieb and Agarwal, 1978; Riener and Edrich, 1999). Measurements were taken for both legs. The same experimenter performed measurements in all subjects. Three recordings were obtained for each joint and each direction (with ~30 s rest between the trials) and the results were averaged across these three recordings.

IV. Non-voluntary air-stepping: The same experimental setup was used as in the protocol II (two-legged suspension system, Fig. 1A). Subjects were instructed to relax and not intervene with movements that might be induced by stimulation. The following stimulation techniques and procedures were used to elicit non-voluntary air-stepping: (i) continuous quadriceps muscle vibration, (ii) responses to passive leg perturbations combined with Jendrassik maneuver, and (iii) aftereffect of a strong long-lasting isometric muscle contraction (Kohnstamm phenomenon). Each experimental condition was repeated three times and about 1–3-min periods of rest were taken between testing probes. The duration of each recording was ~1 min. Since all stimulation procedures were described in detail in our previous study (Selionov et al., 2009) here we describe them only briefly.

(i) Bilateral quadriceps muscle vibration (40–60 Hz, 1-mm amplitude) was produced by small DC motors with an attached eccentric weight. The vibrators were fastened with a rubber belt over the quadriceps tendon of each leg, about 5 cm from the superior border of the patella. Vibration was applied for about 30 s. To minimize voluntary contributions, we also attempted to