Clinical Neurophysiology 115 (2004) 1057–1062

www.elsevier.com/locate/clinph

Cutaneous reflexes from the foot during gait in hereditary spastic paraparesis

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Accepted 4 December 2003

Abstract

Objective: It is known that P2 cutaneous reflexes from the foot show phase-dependent modulation during gait. The role of the motor cortex and the cortico-spinal tract in these reflexes and their modulation is unknown. Patients with hereditary spastic paraparesis (HSP) have a lesion in the cortico-spinal tract and may show deficits in P2 reflexes and/or their modulation.

Methods: Reflex responses of tibialis anterior and biceps femoris after sural nerve stimulation in 10 HSP-patients were compared with those in 10 healthy subjects. The reflexes were studied at two different moments in the step cycle during walking on a treadmill.

Results: Both patients and controls showed a phase-dependent modulation of P2 responses. For the individual muscles, no significant difference in reflex activity was observed between HSP-patients and the controls. However, when all muscles were taken together, the reflex activity for the controls was significantly higher than for the patients.

Conclusions: The results of this study suggest that the cortico-spinal tract is involved in the regulation of the amplitude of the P2 responses and their phase-dependent modulation.
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Keywords: Cutaneous reflexes; Human gait; Hereditary spastic paraparesis (HSP); Sural nerve

1. Introduction

Although the importance of the intact pyramidal system for cutaneous reflexes of the foot is well recognized (Babinski sign) it still is unclear how this system interferes with cutaneous reflexes during normal motor activities such as walking. One important source of afferent input and reflexes during gait comes from the skin of the foot. After electrical stimulation of cutaneous foot afferents, reflex responses appear at a latency of about 80 ms in different muscles of both legs (Hugon, 1973).

During gait these reflexes have been studied in detail (Yang and Stein, 1990; Duysens et al., 1990; Zehr et al., 1997). In intact subjects, the amplitude of these so-called P2 or medium-latency responses is dependent on the phase of the step cycle (Duysens et al., 1990, 1991, 1993; Yang and Stein, 1990; Van Wezel et al., 1997). In neurological patients one often encounters gait abnormalities. It has been suggested that these abnormalities could be partially related to abnormal reflexes or to a deficient regulation of the reflex pathways during gait (Duysens et al., 2000; Jones and Yang, 1994; Zehr et al., 1998). In one study, we studied cutaneous reflex responses during walking of patients who suffer from a predominant loss of large myelinated Aβ fibers (Van Wezel et al., 2000). The reflex responses appeared to be significantly smaller for the patients than for the healthy subjects. Still, the phase dependency of the remaining responses was very similar to that in healthy subjects, indicating an intact control of the remaining cutaneous reflexes. It was concluded that low-threshold Aβ sensory fibers are involved in these reflexes during human gait but the presence of these afferents is not a prerequisite for the modulation, presumably because central sites are involved. A similar conclusion was reached in a study of these reflexes in patients with reflex sympathetic dystrophy (Van der Laan et al., 2000). These two studies are both about the role of peripheral sites on the modulation. Candidates for

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doi:10.1016/j.clinph.2003.12.006

the central sites are the spinal cord (containing the presumed 'central pattern generators' for locomotion) and the cortex. It is well known that there are long loop reflexes, ascending from the spinal cord to various supraspinal structures including motor cortex and from there descending back to the spinal cord (Delwaide et al., 1981). Are these cortical loops involved in reflex modulation?

To answer this type of question, Jones and Yang (1994) used tibial nerve stimulation to study phase-dependent modulation during gait in spastic patients (mildly affected spinal cord injury). They found that phase-dependent modulation was clearly affected (absence of phase-dependent reversal in TA, tibialis anterior). The main difference, in comparison with normal subjects, was an absence of the suppressive responses in TA at end swing. In stroke patients, Zehr et al. (1998) observed that P2 responses were small or absent during walking. However, these responses still showed a phase dependent modulation. These results are consistent with recent findings indicating an intact motor cortex as an important element in these reflexes and their modulation during gait (Christensen et al., 1999; Pijnappels et al., 1998). They showed a facilitation of corticospinal input onto cutaneous reflex pathways after magnetic stimulation of the cortex.

In stroke one seldom has well defined lesions. To study more purely the role of the pyramidal tract it may be preferable to choose genetic models of selective pyramidal disease. Patients with hereditary spastic paraparesis (HSP) – particularly the 'pure' hereditary spastic paraparesis- are known to have almost exclusively a degeneration of the cortico-spinal tract, with only minor and subtle dorsal column involvement. So far, the effect of this degeneration on cutaneous reflexes of the foot has not been studied. In the present study, the differences in reflexes between HSP-patients and healthy subjects were evaluated during gait because it is known that cutaneous reflexes are facilitated during gait as compared to standing (Duysens et al., 1993; Komiyama et al., 2000). Moreover, by studying these reflexes during gait one can learn about their phase-dependent modulation. If modulation persist while the overall reflex amplitude is decreased in HSP then the data are consistent with subcortical sources being dominant in this type of modulation.

2. Methods

Most of the presently used methods have been described elsewhere in detail (Duysens et al., 1990, 1995; Van Wezel et al., 1997; Van der Laan et al., 2000). The essentials are given here, together with some specific procedures.

Ten patients with HSP (6 men, 4 women; age 41 ± 12.6 years (mean ± SD)) were included in this study. The diagnostic criteria for HSP are spasticity of the lower extremities, paresis of the lower extremities (not as clear as the spasticity), hyperreflexia, Babinski sign, and a positive family anamnesis. In addition, a disorder of the sphincter, mild sensory disorders, and hyperreflexia and weakness of the upper extremities can be seen. A control group was made with 10 healthy subjects, without neurological or muscular disorders (8 men, two women; age 26.2 ± 5.1 years). The experimental procedure was approved by the local Ethical Committee and all subjects gave their informed consent. All subjects underwent the same protocol. The HSP-patients were allowed to walk at their preferred velocity. The mean velocity of the patients was 1.6 km/h (SD = 0.6). This low velocity was related to the spasticity of the leg muscles in these patients. The healthy controls found this velocity uncomfortable. They therefore were allowed to walk slightly faster, namely at 2.5 km/h. To determine step cycle characteristics, the subjects had special shoes with contact switches. During the experiments the suralis nerve of the left ankle was stimulated with a bipolar stimulation electrode. The stimulus consisted of 5 rectangular pulses of 1 ms duration at 200 Hz. The intensity of the stimulus was two times the perception threshold (PT). This kind of stimulation activates the low-threshold cutaneous afferents from the sole of the foot. To maintain a constant stimulus throughout the whole step cycle, the electrode was firmly attached to the skin with surgical tape. The experiment did not start until a stable PT was reached after a short training period. The PT was also determined at the end of the experiment to see if it changed throughout the experiment. Electromyographic (EMG) recordings of the reflex responses of the biceps femoris (BF) and the TA were made in both legs by means of pairs of surface electrodes. The EMG signals were preamplified, high-pass filtered (cut-off frequency 3 Hz), full-wave rectified, and low-pass filtered (cut-off frequency 300 Hz). All signals were sampled at 500 Hz.

The stimuli were applied while the subjects were walking on a treadmill. Before each experiment, the step cycle duration of each subject was determined for the chosen gait speed. The moment of application of the stimulus was always at a fixed delay after heel strike. This delay differed for all the subjects. Every subject was stimulated in the early and late swing because previous studies had shown that a phase-dependent reflex reversal can occur at these periods of the step cycle (Duysens et al., 1990; Yang and Stein, 1990). The stimulus delay was chosen so that the stimuli were always given in the same phase of the step cycle for the various subjects (for more details, see Duysens et al., 1990).

For each stimulus condition (phase), 10 trials were sampled along with 10 control samples without stimulation. To obtain the 'pure' reflex response, the mean back-ground EMG had to be subtracted from the stimulus EMG. This means that the background activity, corresponding to the period sampled for the response (in the response time window in the trials with stimulation), was measured in cycles without stimulation and that this activity was subtracted from trials with stimulation.

To specify the difference in reflex activity between HSP-patients and controls after stimulation of the sural nerve, a quantification of the P2 responses was performed. The 'pure' reflex responses, as obtained after the subtraction, were visually inspected and a time-window was set taking the following criteria into account.

1. The windows were set on the responses that occurred at P2 latencies (approximately 80 ms after the stimulation) and lasted for about 30 ms.
2. When a muscle showed little or no response no adequate window could be set. An equivalent measure was required to calculate a population average. In these cases a time window was used which was found (in order of priority) in the same muscle in another condition, in nearby muscles in the same leg or in another subject (Duysens et al., 1996).

The settings corresponding to the beginning of the time window were defined as the latencies. Within the windows the 'area under curve' (AUC) was calculated. For each muscle in each subject the mean AUC was calculated for early and late swing. The amplitudes were normalized to the maximum value in the step cycle (i.e. the maximum spontaneous activity) to allow comparison between subjects and groups.

Statistical analysis was applied using the non-parametric Wilcoxon's Rank Sum Test for independent samples ($P < 0.05$).

2.1. Vibration sensitivity

Vibration sensitivity was tested by means of a vibrator (diameter 2 mm) placed on the region innervated by the sural nerve, on the same place as the stimulation electrode. The vibrator could be placed at different controlled depths in the skin (0, 1, 2, 3, 4, and 5 mm). The duration of each trial was 2 s. In each trial the subject had to report whether the vibration was detected. Per 10 trials, a fraction of correct detected stimuli was calculated.

3. Results

Sural nerve stimulation yielded P2 responses such as shown in Fig. 1, based on EMG recordings of the biceps femoris and tibialis anterior of the ipsilateral leg (BFi and TAi) of one control subject.

Mean latencies of these responses in BFi were 78 ms for both populations (HSP and controls; see Table 1). The duration of the P2 response was slightly longer for the controls than for the patients (not significant). In TAi, in which only two patients exhibited clear responses, latencies were slightly longer, but again the mean duration was shorter for the patients.

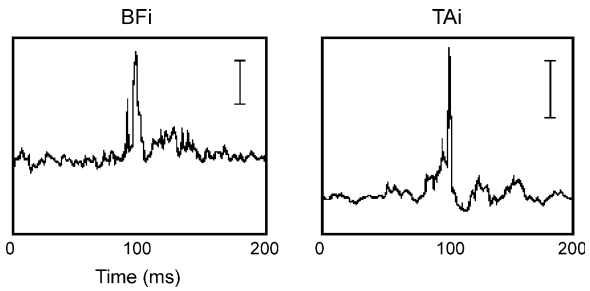

Fig. 1. The reflex responses in ipsilateral biceps femoris (BFi) and tibialis anterior (TAi) of one control subject following stimulation of the sural nerve during walking. EMG calibration, 1 mV. Average of 10 trials.

So far, only latencies and durations of the ipsilateral side are given, because no reflex responses were observed at the contralateral side of the patients, except for one patient in TA. The controls showed crossed reflex activity in all conditions.

3.1. Response amplitude

To measure the response amplitudes, the AUC was calculated in the time window of the responses and the background activity was subtracted (see Section 2). All data were included, even when responses were small. The AUC was normalized to the maximum control value in the step cycle. The responses were obtained at early (es) and late swing (ls) because it is known that the response amplitude can be very different in these periods. To ensure that these phases were indeed comparable in the two groups an analysis was made of the step cycle durations. As mentioned in methods, there was a slight difference in mean walking velocity between the patients and the healthy subjects. This might give differences in the relative swing and stance phase duration. To ensure that the stimulations were given at comparable moments in patients and controls, it was essential to check whether there was a significant difference in step cycle characteristics in the two groups. In the controls the mean swing duration was 38.9% of the step cycle (SD 2.0) while in HSP patients it was 37.6% (SD 6.7). These values were not significantly different (Wilcoxon test, $P = 0.13$).

Table 1
Latencies and duration of detected responses for both HSP-patients and controls

		Latency response (mean ± SD)	Duration response (mean ± SD)
BFi	Controls ($n = 10$)	78 ± 8	34 ± 10
	HSP-patients ($n = 5$)	78 ± 9	27 ± 6
TAi	Controls ($n = 10$)	75 ± 10	32 ± 11
	HSP-patients ($n = 2$)	82 ± 6	23 ± 12

Values were derived from all subjects showing responses in the muscles indicated.

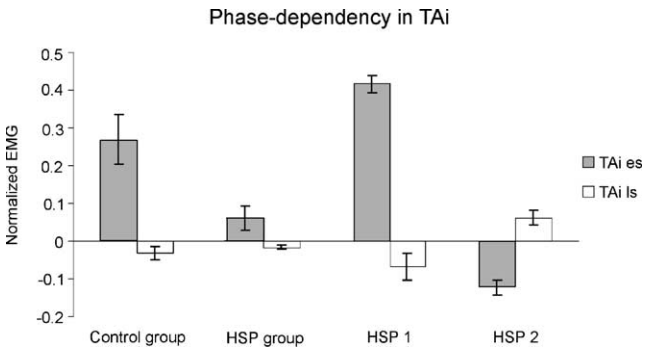

Fig. 2. The normalized AUC in the ipsilateral tibialis anterior (TAi). Shown are the mean values (with standard error) of es (early swing) and ls (late swing) for the control and patient group and for the two patients who showed reflexes separately.

The results of the amplitude analysis for the Tibialis Anterior of the side ipsilateral to stimulation (TAi) are summarized in Fig. 2.

The overall level of the response amplitude in TAi was larger in the control group than in the HSP group, of which only two patients showed clear reflex responses. Furthermore, in both groups, the TAi showed a reflex reversal from facilitation in es to suppression in ls. However, the two patients with clear reflex responses did not show the same reflex pattern. Patient 1 showed a normal pattern, as seen in the control group. In contrast, patient 2 showed much smaller reflex responses and an opposite modulation: a reversal from suppression in es to facilitation in ls.

The overall difference in response amplitude between both groups was also found for most responses measured in the other muscles (see Fig. 3).

For all facilitatory responses, except BFc es, the overall reflex activity in patients was lower than in the control group. The differences within individual muscles were not significant between both groups. However, the difference in overall reflex activity, i.e. the mean values of all 8 muscles together, was statistically significant between groups (Wilcoxon's Signed Rank test, $P = 0.0357$).

3.2. Vibration sensitivity

It is known that HSP-patients have decreased somatosensory sensitivity, due to degeneration of sensory pathways. The question then arises whether the presently observed decrement in reflex responses was due to a deficit in the pyramidal tract or whether it could be attributed to sensory loss, similar to what was observed in patients with sensory neuropathy (Van Wezel et al., 2000).

In general, the controls did not have any difficulty to detect the vibration stimuli at all depths tested. Only at 0 mm depth (i.e. just contact) there were a few subjects who could not detect a number of trials. In contrast, HSP-patients could detect all the stimuli only when the stylus point was at 4 or 5 mm depth. At 0 and 1 mm depth the differences between

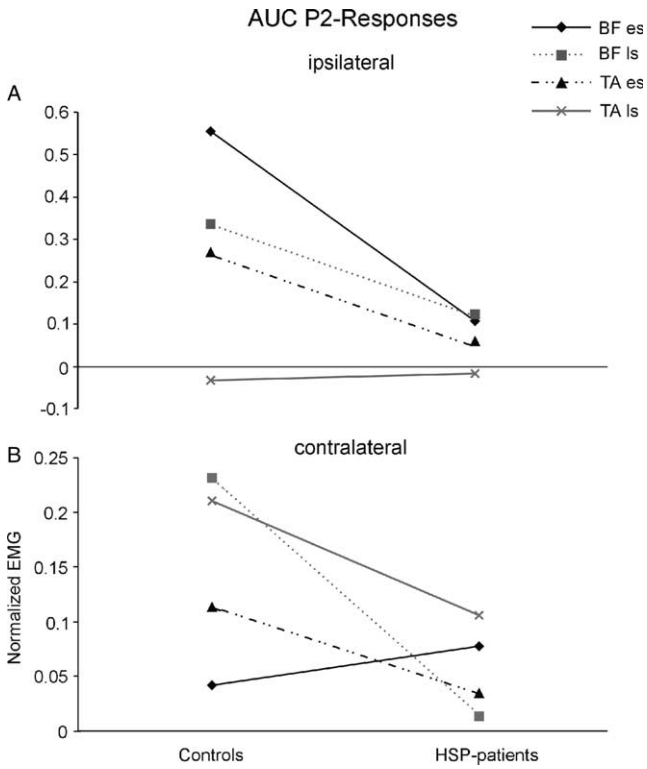

Fig. 3. Means of the AUC of the P2 responses with the AUC as % of the maximum EMG-activity. Shown are mean values of es (early swing) and ls (late swing) in biceps femoris (BF) and tibialis anterior (TA), ipsilateral (3A) and contralateral (3B).

the HSP and the control group were significant ($P = 0.007$ and 0.005, respectively).

To study whether the decrease in reflex amplitude of the HSP-patients was linked to a loss of afferent sensitivity, the values of the P2-peaks of every individual muscle were correlated with the number of correct detected stimuli at each depth.

Only in BFi es a significant positive correlation was observed for a depth of 0 mm ($cc = 0.94$, $P = 0.04$). In contrast, TAc ls (at 0 mm depth) and TAi es (at 1 mm) showed significant negative correlations ($cc = -0.86$, $P = 0.01$ and $cc = -0.81$, $P = 0.03$, respectively). The latter would suggest that low sensitivity could not explain low amplitudes of reflex responses since the lower the vibration sensitivity the higher the reflex responses.

4. Discussion

The main findings of the present study are that HSP patients show less cutaneously induced P2 reflexes and that these reflexes have an unchanged latency and a decreased amplitude as compared to controls. These are novel findings. Except for BFc in early swing, every muscle showed larger reflex activity for the controls. While the data for individual muscles did not reach significance, the mean

activity of all muscles taken together showed a significant decline in HSP.

One may ask whether the decrease in reflex activity was caused by a peripheral deficit (as found earlier for another group of patients, see Van Wezel et al., 2000). However, earlier studies showed that there were no abnormal findings in sensory and motor nerve conduction in HSP-patients (Bruyn et al., 1994; Schady et al., 1991; Thomas et al., 1981). Therefore, it is unlikely that disorders of the peripheral nerves are the cause of the decrease in reflex activity in HSP-patients. In contrast, central motor conduction times have been reported by several authors to show either unrecordable, or delayed responses from the lower limbs (Pelosi et al., 1991; Schady et al., 1991). Also cortical somatosensory evoked potentials (SSEPs) upon tibial nerve stimulations were significantly reduced (Bruyn et al., 1994; Pelosi et al., 1991). Several studies described vibration deficits in patients with HSP (Bruyn et al., 1994; Pelosi et al., 1991; Schady and Sheard, 1990). Vibration sensitivity is mediated by the medial lemniscal system, which passes the dorsal column. Degeneration of the dorsal column is probably the cause of the decrease in percentage of correct detected vibration stimuli, as seen in HSP-patients. In principle, the presently described decrease in reflex activity could be caused by a deficit in this sensory pathway (as a link in long loop reflexes). The vibration deficits in the present study did correlate with a decrease in response amplitude only for one of the muscles investigated (BFi) and, in fact, for other muscles there was a negative correlation. It is therefore unlikely that the sensory deficit is sufficient to explain the current decrease in response amplitude.

More likely is the possibility that the pyramidal tract is involved either because this pathway is part of the long loop of the reflex or because facilitation from this pathway is essential for interneurones involved in the P2 reflex. There have been several studies which have emphasized the importance of the motor cortex for P2 responses. Using magnetic stimulation of the cortex it was found that motor evoked potentials (MEPs) evoked by magnetic stimulation of the cortex were more facilitated by prior sural-nerve stimulation than the algebraic sum of the control MEP and the cutaneous facilitation in the EMG when evoked separately (Pijnappels et al., 1998; Christensen et al., 1999). In contrast, electrical evoked MEPs were not facilitated by prior stimulation of the sural nerve (Christensen et al., 1999). A lack of facilitation of the H-reflex was found as well. These results were interpreted as suggesting that a transcortical pathway may contribute to P2 cutaneous reflexes during walking. The present study further supports this notion and adds to other studies showing that lesions of the pyramidal tract affect P2 responses.

A final result is the difference in reflex modulation in some HSP patients as compared to healthy subjects. The mean reflex response of the total group of patients showed the same modulation as that of the healthy subjects, only with a smaller amplitude. However, for the individual patients, the modulation differed sometimes. For example, one of the two patients with clear reflex responses in TAi showed normal responses, while the other showed weak opposite responses as compared to healthy subjects. It seemed that the modulation of the reflex responses of the patients was related to the walking performance: patients with a more asymmetric walking pattern showed more often a different reflex modulation (as patient 2), in comparison with healthy subjects. Patients with a less affected walking pattern, e.g. patient 1, showed more equal reflex behaviour as compared to healthy subjects. However, this can not be shown statistically and this hypothesis needs further investigation.

At first sight this result is in line with those obtained in other studies on patients with lesions of the pyramidal tract. In patients with stroke, it was found that P2-responses following peroneal nerve stimulation were mostly suppressive during the swing phase and that a reversal was absent (Zehr et al., 1998). Jones and Yang (1994), using tibial nerve stimulation in mildly affected SCI patients, found mostly facilitatory responses and an absence of reflex reversal at end swing. Therefore, it can be concluded that the cortico-spinal tract is probably involved in the regulation of the amplitude of the P2 responses and their phase-dependent modulation.

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