Modulation of presynaptic inhibition and disynaptic reciprocal Ia inhibition during voluntary movement in spasticity

H. Morita,* C. Crone, † D. Christenhuis, N. T. Petersen and J. B. Nielsen

Division of Neurophysiology, Department of Medical Physiology, The Panum Institute, Copenhagen University, Blegdamsvej, Copenhagen, Denmark

Summary
The aim of the study was to investigate whether impaired control of transmission in spinal inhibitory pathways contributes to the functional disability of patients with spasticity. To this end, transmission in the pathways mediating disynaptic reciprocal Ia inhibition and presynaptic inhibition was investigated in 23 healthy subjects and 20 patients with spastic multiple sclerosis during ankle dorsiflexion and plantar flexion. In healthy subjects, but not in spastic patients, the soleus H reflex was depressed at the onset of dorsiflexion (300 ms rise time, 20% of maximal voluntary effort). At the onset of plantar flexion, the soleus H reflex was more facilitated in the healthy subjects than in the patients. The H reflex increased more with increasing level of tonic plantar flexion and decreased more with dorsiflexion in the healthy subjects than in the spastic patients. Transmission in the disynaptic Ia reciprocal inhibitory pathway from ankle dorsiflexors to plantar flexors was investigated by conditioning the soleus H reflex by previous stimulation of the common peroneal nerve (conditioning-test interval 2–3 ms; stimulation intensity 1.05 times the motor response threshold). At the onset of dorsiflexion, stimulation of the common peroneal nerve evoked a significantly larger inhibition than at rest in the healthy subjects but not in the spastic patients. At the onset of plantar flexion the inhibition decreased in the healthy subjects, but because only weak inhibition was observed at rest in the patients it was not possible to determine whether a similar decrease occurred in this group. There were no differences in the modulation of inhibition during tonic plantar flexion and dorsiflexion in the two populations. Presynaptic inhibition of Ia afferents terminating on soleus motor neurones was evaluated from the monosynaptic Ia facilitation of the soleus H reflex evoked by femoral nerve stimulation. Femoral nerve facilitation was decreased at the onset of dorsiflexion and increased at the onset of plantar flexion in the healthy subjects and patients, but the changes were significantly greater in the healthy subjects. There was no difference between the two populations in the modulation of presynaptic inhibition during tonic plantar flexion and dorsiflexion. It is suggested that the abnormal regulation of disynaptic reciprocal inhibition and presynaptic inhibition in patients with spasticity is responsible for the abnormal modulation of stretch reflexes in relation to voluntary movement in these patients. Lack of an increase in reciprocal inhibition and presynaptic inhibition at the onset of dorsiflexion may be responsible for the tendency to elicitation of unwanted stretch reflex activity and co-contraction of antagonistic muscles in patients with spasticity.

Keywords: spasticity; reciprocal inhibition; presynaptic inhibition; H reflex; voluntary movement

Abbreviations: CPN = common peroneal nerve; FN = femoral nerve; MT = motor response threshold

© Oxford University Press 2001
Introduction

Spasticity is characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) and exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neurone syndrome (Lance, 1980). There has been some debate during the last 5–10 years about the significance of spasticity for the functional disability of the patients. Several studies of the lower extremities have found that stretch reflex activity in antagonistic muscles may counteract voluntary movements in patients with spasticity (Dimitrijevic and Nathan, 1967; Mizrahi and Angel, 1979; Benecke et al., 1983; Corcos et al., 1986; Knutsson et al., 1997). Furthermore, co-contraction of antagonistic muscles has been found in spastic gait (Knutsson and Richards, 1979; Knutsson and Mårtensson, 1980) and in relation to ankle dorsiflexion movements in patients with spastic hemiplegia (Levin and Hui-Chan, 1994).

During voluntary movements in healthy subjects, the excitability of antagonistic α motor neurones is controlled by central modulation of spinal inhibitory pathways (Iles, 1986; Crone et al., 1987; Crone and Nielsen, 1989a; Nielsen and Kagamihara, 1992). Deficient modulation of these inhibitory pathways could explain, at least partly, the uncoordinated contraction/relaxation of agonist/antagonist muscles that is seen in patients with spasticity. Several inhibitory mechanisms have been studied in patients with spasticity at rest, including presynaptic inhibition (Faist et al., 1994; Nielsen et al., 1995), postactivation depression (Nielsen et al., 1995), disynaptic reciprocal Ia inhibition (Crone et al., 1994), recurrent inhibition (Mazzocchio and Rossi, 1997) and Ib inhibition (Delwaide and Olivier, 1988). In general, all the inhibitory mechanisms have been found to be decreased to a variable extent in patients with spasticity, which suggests that impaired control of the interneurones through which the inhibitory effects are mediated contributes to the hyperexcitability of the stretch reflexes, at least in the resting state. However, these studies have not allowed any conclusion to be made about whether the decreased inhibition that is seen at rest has any functional significance for the motor performance of patients with spasticity.

The aim of the present study was to compare the abilities of patients with spasticity and healthy subjects to modulate transmission in the spinal inhibitory pathways during voluntary movements, as a first step in the attempt to elucidate whether the impaired ability to perform smooth and coordinated movements in spasticity can be explained by impaired central modulation of spinal inhibitory pathways.

Four variables were tested (Fig. 1): (i) the soleus H reflex; (ii) disynaptic reciprocal Ia inhibition of the soleus H reflex (Crone et al., 1987); (iii) the inhibition of the soleus H reflex that is evoked by a conditioning stimulus to the common peroneal nerve (CPN) at a conditioning–test interval of 15–20 ms, termed the D1 phase, which is presumed to represent presynaptic inhibition (Mizuno et al., 1971); and (iv) presynaptic inhibition of quadriceps Ia afferent fibres terminating on soleus motor neurones. The last variable was evaluated by the indirect method described by Hultborn and colleagues (Hultborn et al., 1987a, b), in which the femoral nerve (FN) is stimulated at the femoral triangle and this stimulation facilitates the soleus H reflex, which is monosynaptic within the initial 0.5 ms. Any change in the size of this facilitation reflects a change in presynaptic inhibition of the afferent fibres of the FN and there is reason to believe that this change in inhibition parallels the change in presynaptic inhibition of soleus Ia afferent fibres (Hultborn et al., 1987a, b). These four variables were examined during the tonic and dynamic phases of the dorsiflexion and plantar flexion movements of the ankle.

Subjects and methods

Twenty patients with a long-standing diagnosis of multiple sclerosis (aged 29–61 years, mean ± SD, 46 ± 10 years) and 23 healthy control subjects (aged 21–63 years, 37 ± 12 years) were examined. According to the Declaration of Helsinki, all gave informed consent to the examination, which was approved by the local Ethics Committee of Bornholm, Frederiksborg, Roskilde, Storstrøm and Vestskeland. All patients were evaluated clinically (Table 1). None of the patients received any antispastic medication. Three of them showed spasticity on the examined side only, whereas the rest showed spasticity on both sides. In these cases the most affected side was studied. The healthy subjects had no signs or symptoms of neurological or other disease and had no history of neurological disease.

The subjects were seated in an armchair with the leg to be examined semiflexed at the hip (120°), the knee flexed to 160° and the ankle in 110° plantar flexion. The foot was mounted on a foot-plate that was connected to a torque meter, and the torque was displayed on an oscilloscope placed in front of the subject. Surface electrodes were used for stimulation and recording.

H reflex

The soleus H reflex was evoked by stimulating the tibial nerve through a monopolar stimulating electrode (1 ms rectangular pulse). The reflex response was measured as the peak-to-peak amplitude of the non-rectified reflex. The reflexes were recorded by disc electrodes placed over the soleus muscle. The sensitivity of the H reflex to facilitatory and inhibitory conditioning effects has been shown to depend crucially on its size (Crone et al., 1990). Hence, when measuring the effects of conditioning stimuli, the size of the test reflex was kept at 20–25% of the maximal motor response ($M_{max}$). When the natural inhibition of the soleus H reflex was being evaluated, the reflex was adjusted to 20–25% of $M_{max}$ at rest, and this stimulation strength was kept constant during the movements. To ensure that there was no
Fig. 1 Experimental setup. (A) The soleus H reflex was evoked by stimulation of the tibial nerve in the popliteal fossa (Test TN) and conditioned by stimulation of either the common peroneal nerve (Cond. 1, CPN) or the femoral nerve (Cond. 2, FN). CPN stimulation activates interneurones that mediate reciprocal Ia inhibition of soleus motor neurones. In healthy subjects this inhibition may be seen as a depression of the soleus H reflex after CPN stimulation at conditioning–test intervals of ~2–4 ms. At longer conditioning–test intervals (~10–30 ms), a second period of inhibition is seen, which has been termed D1 and is probably caused by presynaptic inhibition of soleus Ia afferents. Panel B shows an example of these two inhibitions from a healthy subject (open circles). For comparison, data from a typical spastic multiple sclerosis patient are shown (closed circles). Reciprocal Ia inhibition was generally measured at a conditioning–test interval of 2–3 ms and the D1 inhibition at an interval of 15 ms. The intensity of the CPN stimulation was adjusted to 1.05 times the motor threshold in the tibialis anterior muscle. FN stimulation activates Ia afferents, which have heteronymous monosynaptic projections to soleus motor neurones and may therefore lead to facilitation of the soleus H reflex after a short delay. This is shown in panel C for a healthy subject (open circles) and a spastic patient (closed circles). The negative conditioning–test intervals indicate that the test TN stimulation was applied before the conditioning FN stimulation. The difference in the latency of facilitation in the two subjects can probably be explained by differences in body height and/or peripheral conduction velocity. The degree of facilitation was measured within the initial 0.5 ms after its onset in both healthy and spastic patients.

displacement of stimulating electrodes during movement, the size of a small M response (evoked by a separate stimulus that was stronger than that which evoked the H reflex) was measured throughout the experiment. These measurements were intermingled randomly with H reflex measurements. Each measurement was repeated every 4 s.

Conditioning stimulation
The soleus H reflex was conditioned by stimulation of either the CPN or the FN.

Stimulation of the common peroneal nerve
The CPN was stimulated (rectangular 1 ms pulse) by bipolar surface electrodes placed distal to the neck of the fibula at a position where the threshold for the motor response in the tibialis anterior muscle was lower than the threshold for the motor response in the peroneal muscles. The stimulus strength was expressed in multiples of the motor response threshold (MT) in the tibialis anterior muscle. Figure 1B shows a typical time course of the effect of CPN stimulation on the soleus H reflex in a healthy subject (open circles) and a patient with multiple sclerosis (closed circles). In most resting healthy subjects, such as the subject illustrated in Fig. 1B, CPN stimulation produces significant depression of the soleus H reflex at a conditioning–test interval of 2–3 ms (Crone et al., 1987). This depression has been shown to be mediated probably by the disynaptic Ia inhibitory pathway and it is possible, by measuring the size of the inhibition during voluntary movements, to obtain indirect evidence of transmission in this pathway (Crone and Nielsen, 1994). In most multiple sclerosis patients with spasticity, such as the patient illustrated in Fig. 1B, this disynaptic reciprocal inhibition is not present and is replaced by a later-occurring facilitation (Crone et al., 1994). The interest of the present
Table 1 Clinical data of the patients with spastic multiple sclerosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Muscle power</th>
<th>Muscle resistance</th>
<th>Achilles reflex</th>
<th>Clonus</th>
<th>H_{max}/M_{max} (%)</th>
<th>H-reflex modulation</th>
<th>Reciprocal inhibition</th>
<th>D1 inhibition</th>
<th>Fn facilitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>70</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>50</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>75</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>25</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>70</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>35</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>78</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>70</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>80</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>60</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>57</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>71</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>43</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>38</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>80</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>29</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>42</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>57</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>35</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>50</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>90</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>57</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>35</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>18</td>
<td>52</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>80</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>19</td>
<td>38</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>20</td>
<td>42</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Twenty patients, aged 29–61 years, were investigated. Ankle dorsiflexion and plantar flexion muscle power, muscle resistance, the Achilles reflex and clonus were evaluated and scaled for each patient. Muscle power was recorded as Daniel’s manual muscle test (MMT) score: 5 = normal; 4 = 50% of normal muscle power; 3 = could contract against gravity; 2 = contraction possible, but not against gravity; 1 = some contraction was possible without any joint movement; 0 = no muscle contraction. Muscle resistance was scored as follows: 0 = normal; 1 = small increase; 2 = moderate increase compared with normal; 3 = strong increase compared with normal. The Achilles reflex was scored as follows: 0 = normal; 1 = small increase; 2 = moderate increase; 3 = strong increase compared with normal. Clonus was scored as follows: 0 = no clonus; 1 = fewer than five extra beats; 2 = weak clonus; 3 = sustained clonus. The remaining columns give the value of \( H_{\text{max}} \) as a percentage of \( M_{\text{max}} \) and show whether H-reflex modulation, reciprocal inhibition, D1 inhibition and FN facilitation were investigated as part of the study.

Study was to compare the modulation of transmission in the disynaptic reciprocal inhibitory pathway during voluntary movement (see below) in healthy subjects and patients with spasticity. For this purpose, the depression of the soleus H reflex by stimulation of the CPN was measured at the conditioning–test interval at which the largest amount of inhibition was observed at rest (conditioning–test interval of 2–3 ms). In subjects (in particular the patients with spasticity) in whom no inhibition was observed at rest, a conditioning–test interval of 2 ms was chosen. The intensity of the CPN stimulation was kept at 1.05 \( \times \) MT throughout all experiments. The constancy of CPN stimulation was checked by monitoring a small motor response evoked by the stimulation in the tibialis anterior EMG.

At conditioning–test intervals longer than 8–10 ms, CPN stimulation evokes a second inhibition in healthy subjects (Fig. 1B). This inhibition has been termed D1 (Mizuno et al., 1971) and it is believed to be caused by presynaptic inhibition of the terminals of Ia afferents on soleus motor neurones. The lack of D1 in patients with spasticity (Fig. 1B, closed circles) supports the view that presynaptic inhibition is decreased in patients with spasticity (Faist et al., 1994; Nielsen et al., 1995).

Stimulation of the femoral nerve

The FN was stimulated by a monopolar ball electrode placed in the femoral triangle. The indifferent electrode was placed at the posterior aspect of the upper thigh, just below the gluteus maximus muscle. The intensity was adjusted to be just above the threshold for the motor response in the quadriceps muscle (1.1 \( \times \) MT). A time course of the effect of the FN facilitation on the soleus H reflex was obtained in each experiment. Figure 1C shows typical examples of time courses from a healthy subject (open circles) and a spastic patient (closed circles). The difference in latency of facilitation in the two subjects probably results from different body height and a difference in nerve conduction velocity. In general, there was no difference in the latency of facilitation in healthy subjects and patients with spasticity (see also Faist et al., 1994; Nielsen et al., 1995). The onset of facilitation was taken to be the earliest conditioning–test interval at which the conditioned reflex was at least 5% larger than the control reflex and the conditioning–test interval used throughout the experiment was 0.5–1 ms longer than this. The size of the facilitation measured at this conditioning–test interval reflects the size of the monosynaptic excitatory postsynaptic potential in the soleus motor neurones evoked by activation of quadriceps Ia afferent fibres and changes in
its size are considered to reflect changes in the presynaptic inhibition of these afferents (Hultborn et al., 1987a, b). This may provide evidence of the modulation of presynaptic inhibition of soleus Ia afferents also, as presynaptic inhibition of quadriceps and soleus Ia afferents on the same motor neurones is believed to be controlled in parallel (Hultborn et al., 1987b). The FN facilitation of the soleus H reflex was measured in addition to measurement of the D1 inhibition evoked by CPN stimulation for two reasons. First, the FN facilitation reflects the level of ongoing presynaptic inhibition of the Ia afferents, whereas the D1 inhibition reflects presynaptic inhibition evoked by peripheral nerve stimulation. Secondly, the two measures provide independent evidence of presynaptic inhibition and help to exclude the possibility that changes in recruitment gain within the soleus motor neurone pool can explain the observations (Nielsen and Kagamihara, 1993b). Increased D1 inhibition might thus be explained both by increased presynaptic inhibition and by increased recruitment gain. Increased presynaptic inhibition would be seen as decreased FN facilitation, whereas increased recruitment gain would be seen as increased FN facilitation. Therefore, it is only when opposite changes in D1 inhibition and FN facilitation are observed that the changes may be explained by changes in presynaptic inhibition. This was the case for the experiments in this study, and we may therefore exclude recruitment gain as an explanation of our observations.

**Voluntary motor tasks**

At the start of each experiment, the maximal tonic dorsiflexion and plantar flexion effort that could be maintained for ~15 s was measured. The contraction level during the actual experiments was expressed as a percentage of this contraction level.

The modulation of the H reflex, disynaptic reciprocal Ia inhibition, D1 inhibition and FN facilitation were investigated in the following situations.

**Rest**

A time course of the different conditioning stimuli was obtained at rest at the beginning of each experiment, as explained above. When the proper conditioning–test intervals had been determined, the measurements at these intervals were repeated. Furthermore, control measurements at rest were randomly intermingled with the measurements during contraction.

**Tonic isometric dorsiflexion and plantar flexion**

The torque was displayed on an oscilloscope as a continuous line and the subject was asked to maintain steady tonic isometric dorsiflexion or plantar flexion by superimposing the torque line on a preset horizontal target line, which corresponded to 10, 20, 30 and 40% of the maximal dorsiflexion or plantar flexion effort. Each measurement usually lasted ~5 min. If the subject experienced any fatigue within this time, the measurements were paused and the subject was allowed to relax for ~5 min.

**Dynamic ramp-and-hold dorsiflexion and plantar flexion**

The torque was displayed at a slow sweep speed on the oscilloscope, and the subject was asked to follow a ramp drawn on the oscilloscope screen. The subject initiated the contraction in response to an auditory starter signal presented approximately every 4 s and the conditioning and test stimuli were set in relation to the start of EMG activity in the contracting muscle. Measurements were made at the onset of EMG activity and at the end of the ramp phase of the contraction. The ramp phase lasted 300 ms and the hold phase ~1 s. The torque level during the hold phase was set to 20% of the maximal voluntary dorsiflexion or plantar flexion effort.

**Data analysis**

The data were stored on a computer for later statistical analysis. The mean and standard error of the mean were calculated on-line for all reflex responses. Differences in the sizes of conditioned and control reflexes were tested by analysis of variance. Differences in the population average of the reflexes were tested by analysis of variance.

**Results**

As seen in Table 1, almost all the patients had normal muscle power in the leg that was examined and their maximal voluntary dorsiflexion and plantar flexion efforts fell within the normal range. All the patients were thus able to perform the required voluntary motor tasks, although with varying difficulty. On visual inspection, there was no difference in the way that the patients and the healthy subjects performed ramp-and-hold contractions and there was no evidence of co-contraction of antagonistic muscles in any of the patients during the tasks. In the following we express the data as percentages of the maximal voluntary dorsiflexion or plantar flexion effort. Because almost all spastic patients had normal dorsiflexion and plantar flexion strength, expressing the data in absolute torque values would not have changed the results.

**H-reflex modulation**

The value of $H_{\text{max}}/M_{\text{max}}$ ($H_{\text{max}}$ is the maximal H reflex) in the multiple sclerosis patients was larger than in the healthy control subjects at rest (57 ± 22 versus 44 ± 23%), but this difference was not statistically significant ($P = 0.06$). This
is in accordance with our previous findings (Crone et al., 1994; Nielsen et al., 1995).

In eight patients and 18 healthy subjects, the modulation of the H reflex during tonic isometric dorsiflexion and plantar flexion was investigated. The population average of the H reflex recordings from these subjects is illustrated in Fig. 2A. At rest the size of the H reflex was adjusted to ~20% of $M_{\text{max}}$ [(21 ± 6% of $M_{\text{max}}$ for the healthy subjects and 23 ± 8% of $M_{\text{max}}$ for the patients ($P > 0.2$)].

**Tonic contractions**

During dorsiflexion, the H reflex decreased in the healthy subjects (Fig. 2A, open circles). The H reflex was already significantly reduced at 10% of maximal dorsiflexion effort, and at 40% of the maximal dorsiflexion effort the H reflex was only 8.3 ± 6.3% of $M_{\text{max}}$, which was a highly significant reduction compared with rest ($P < 0.001$). In the patients, however, the H reflex was not even significantly reduced at 40% of maximal dorsiflexion effort compared with rest (Fig. 2A, closed circles). At this level of contraction the H reflex was thus also significantly less reduced in the spastic subjects than in the healthy subjects ($P < 0.001$).

During plantar flexion, an increase in the soleus H reflex was seen in healthy subjects and in patients. In healthy subjects, the H reflex was increased to 44 ± 15% of $M_{\text{max}}$ at a maximal plantar flexion effort of 40% of maximal strength, which is a highly significant increase compared with rest ($P < 0.001$; Fig. 2A, open circles). An increase in the H reflex during plantar flexion was also observed in the patients (Fig. 2A, closed circles), but it was less marked than in the healthy subjects. At 10–30% of maximal voluntary plantar flexion effort, the H reflex was thus significantly less facilitated in the patients with spasticity than in the healthy subjects ($P < 0.05$). However, at 40% of maximal voluntary plantar flexion effort there was no statistically significant difference in the size of the reflex in the two populations.

Seven of the eight patients had normal voluntary strength in both plantar flexor and dorsiflexor muscles. Omitting the last patient, in whom a reduction of the maximal voluntary dorsiflexion and plantar flexion effort to around 50% was found, did not alter the findings.

**Ramp-and-hold contraction**

The modulation of the soleus H reflex was also investigated in the dynamic phase and at the end of a fast ramp-and-hold dorsiflexion and plantar flexion in 17 healthy subjects and 14 patients (ramp lasting 300 ms; Fig. 2B). The size of the H reflex at rest was adjusted to 22.5 ± 8.0% of $M_{\text{max}}$ in the patients and 20.5 ± 4.5% of $M_{\text{max}}$ in the healthy subjects. At the onset of dorsiflexion the H reflex was depressed in the healthy subjects to 13.0 ± 8.4% of $M_{\text{max}}$ ($P < 0.001$), whereas the H reflex was not significantly decreased in the patients with spasticity (21.5 ± 8.5%). At the onset of plantar flexion, the soleus H reflex was strongly facilitated in both groups, to 51.8 ± 18.4% of $M_{\text{max}}$ in healthy subjects and to 40.1 ± 20.8% of $M_{\text{max}}$ in the patients. However, the increase was significantly larger in the healthy subjects than in the patients ($P < 0.05$). Towards the end of the ramp phase of the dorsiflexion (300 ms after movement onset), the H reflex was even more strongly depressed in the healthy subjects (to 12 ± 10.6% of $M_{\text{max}}$), whereas only a small depression (to 19.8 ± 7.8% of $M_{\text{max}}$) was observed in the
patients. The H reflex was thus still significantly more depressed 300 ms after the onset of dorsiflexion in the healthy subjects than in the patients ($P < 0.01$). Towards the end of the plantar flexion ramp, the H reflex was significantly smaller than at the onset of movement in the healthy subjects (onset, $51.7 \pm 10.9\%$ of $M_{\text{max}}$; end, $40.8 \pm 10.9\%$ of $M_{\text{max}}$; $P < 0.05$), whereas there was no significant difference for the patients with spasticity (onset, $40.1 \pm 20.8\%$ of $M_{\text{max}}$; end, $44.0 \pm 26.6\%$ of $M_{\text{max}}$). Four of the 14 patients with spasticity had a clearly reduced maximal voluntary strength in the ankle dorsiflexion and/or plantar flexors. Omitting data from these subjects had no qualitative influence on the findings.

**Modulation of disynaptic reciprocal inhibition**

**Tonic contractions**

In seven patients with spasticity and 11 healthy subjects, the effect of CPN stimulation ($1.0 \times MT$) on the soleus H reflex at a conditioning–test interval of 2 ms was evaluated during tonic dorsiflexion and plantar flexion.

Figure 3A illustrates the population average of the measurements. In the healthy subjects (open circles), the amount of inhibition of the H reflex decreased with plantar flexion (only significant at 40% of maximal voluntary plantar flexion effort; $P < 0.05$), whereas there was no change in the amount of inhibition during dorsiflexion, which confirms previous findings (Iles, 1986; Crone et al., 1987). In the patients with spasticity (closed circles) a similar pattern was seen, but the decrease in inhibition during plantar flexion was not statistically significant compared with rest at any of the contraction levels.

**Ramp-and-hold contraction**

The modulation of inhibition was investigated in relation to ramp-and-hold dorsiflexion and plantar flexion in 15 patients with spasticity and 19 healthy subjects (Fig. 3B). In the healthy subjects (open circles), the amount of inhibition was strongly increased at the onset of dorsiflexion ($P < 0.01$) and strongly decreased at the onset of plantar flexion ($P < 0.01$). However, towards the end of the ramp phase there was no difference in the amount of inhibition compared with rest for either dorsiflexion or plantar flexion. In the patients with spasticity (closed circles) a significant decrease of inhibition was also seen at the onset of plantar flexion ($P < 0.01$), but there was no change in the amount of inhibition at the onset of a fast dorsiflexion. As in the healthy subjects, there was no difference between the amount of inhibition towards the end of the ramp contractions compared with rest.

CPN stimulation in general produced a larger depression of the H reflex in the healthy subjects than in the patients with spasticity at rest, which has also been found previously (Crone et al., 1994). To make sure that the difference in regulation of the inhibition at the onset of the fast dorsiflexion could not be related to the difference in the amount of inhibition at rest, we also compared the modulation of inhibition at rest with the modulation at the onset of dorsiflexion in the subpopulation of healthy subjects in whom no inhibition was observed at rest ($n = 6$). Data from these subjects are shown as open triangles in Fig. 3B. It can be seen that there was also a significant increase in inhibition at the onset of dorsiflexion compared with rest in these subjects ($P < 0.001$).

Omitting the data from the five subjects who were not able to produce a maximal voluntary dorsiflexion or plantar flexion within the normal range did not change the results.
Modulation of presynaptic inhibition of Ia afferents

D1 inhibition

Figure 4 illustrates the modulation of the effect of CPN stimulation on the soleus H reflex at an interval of 15–20 ms during tonic dorsiflexion and plantar flexion (Fig. 4A) and in relation to fast ramp-and-hold dorsiflexion and plantar flexion (Fig. 4B). The experiments with ramp-and-hold plantar flexion were performed in seven healthy subjects and 11 patients with spasticity. The experiments in relation to tonic contraction were performed in the same seven healthy subjects but in only six patients with spasticity.

At rest, the D1 inhibition was significantly more pronounced in the healthy subjects than in the patients with spasticity (P < 0.01). It was not possible in any of the 11 patients with spasticity to evoke a significant D1 inhibition at any conditioning–test interval between 15 and 20 ms, whereas this was possible in all but two of the healthy subjects. Except for a small but non-significant decrease in inhibition at the onset of plantar flexion (Fig. 4B, closed circles), there was no observable modulation of the inhibition during any of the tasks in the patients with spasticity. In the healthy subjects, a small but non-significant decrease in inhibition was seen in relation to tonic plantar flexion, whereas there was no change in the amount of inhibition during tonic dorsiflexion in relation to rest (Fig. 4A, open circles). At the onset of plantar flexion a decrease in inhibition was observed, which was just significant (P < 0.05). At the end of the ramp phase of plantar flexion the inhibition was still smaller than at rest, but this difference was not significant. There was no change in the amount of inhibition at the onset or end of dorsiflexion.

Averaged data from the two subjects in whom only a small D1 inhibition was evoked at rest are shown as open triangles in Fig. 4B. In both subjects a decrease of inhibition was observed in relation to plantar flexion and an increase in relation to dorsiflexion.

Omitting the data from the four subjects who had decreased maximal voluntary dorsiflexion or plantar flexion effort did not change the results.

Femoral nerve facilitation

In nine healthy subjects and seven patients with spasticity, modulation of the short-latency facilitation of the soleus H reflex evoked by stimulation of the FN was investigated during the different tasks (Fig. 5). Only subjects in whom >110% facilitation at rest could be evoked were included.

Tonic contractions

In the healthy subjects, facilitation decreased during tonic dorsiflexion [a finding that has been described previously (Crone and Nielsen, 1989a)] and the facilitation was significantly smaller at 40% of the maximal voluntary dorsiflexion effort than at rest (P < 0.05). During tonic plantar flexion (Fig. 5A) there was no clear change in the degree of facilitation, a finding which has also been described previously (Meunier and Pierrot-Deseilligny, 1989; Nielsen and Kagamihara, 1993a; Nielsen, 1995). In the patients with spasticity there was no significant change in the degree of facilitation during either dorsiflexion or plantar flexion, although the facilitation tended to be smaller during plantar flexion than at rest (P = 0.06).

Ramp-and-hold contraction

In the healthy subjects, the facilitation increased at the onset of ramp-and-hold plantar flexion (P < 0.001) and decreased at the onset of the ramp-and-hold dorsiflexion (P < 0.05), as shown in Fig. 5B. Similar findings have been described previously by Hultborn and colleagues (Hultborn et al., 1987b) and Meunier and Pierrot-Deseilligny (Meunier and Pierrot-Deseilligny, 1989). Towards the end of the ramp phase, the degree of facilitation was similar to that at rest. A similar decrease in facilitation during the ramp phase of
within the time course of postactivation depression (Crone In healthy subjects, the depression of the soleus H reflex is small or absent in patients with spasticity (Nielsen et al., 1992). However, postactivation depression is small or absent in patients with spasticity (Nielsen et al., 1995). It is therefore not likely that the smaller amount of disynaptic reciprocal inhibition evoked at the onset of dorsiflexion in patients with spasticity is caused by greater depression of transmission in this pathway because of its previous activation in the preceding movement. The lack of decrease of presynaptic inhibition at the onset of plantar flexion would also be difficult to explain by changes in postactivation depression evoked by the preceding contraction.

**Regulation in relation to dorsiflexion**

A lack of depression of the H reflex in relation to dorsiflexion in patients with spasticity has been demonstrated in several previous studies. Pierrot-Deseilligny and Lacert were, to our knowledge, the first to demonstrate reduced H reflex depression at the onset of ankle dorsiflexion in spastic patients (Pierrot-Deseilligny and Lacert, 1973). Later, Boorman and colleagues described reduced soleus H reflex depression during isometric dorsiflexion in patients with incomplete spinal cord injury (Boorman et al., 1996). Earlier, Boorman and colleagues had found reduced depression of the soleus H reflex in spinal cord-injured patients during dorsiflexion of the foot while pedalling (Boorman et al., 1992), and Sinkjaer and colleagues found that the H reflex was less depressed in the swing phase of walking in patients with spasticity and multiple sclerosis (Sinkjaer et al., 1996). The present study extends these studies by demonstrating that failure to depress the soleus H reflex in spastic multiple sclerosis patients is particularly a problem at the onset of fast dorsiflexion. A much clearer difference between healthy subjects and patients was seen at the onset of dorsiflexion compared with tonic dorsiflexion.

In healthy subjects, the depression of the soleus H reflex in relation to ankle dorsiflexion is probably caused by a combination of postsynaptic and presynaptic inhibitory mechanisms (Crone et al., 1987; Crone and Nielsen, 1989a). Before and at the onset of contraction, the depression of the H reflex is in all likelihood caused by a central descending command to the interneurones mediating disynaptic reciprocal inhibition as well as to interneurones mediating presynaptic inhibition of soleus Ia afferents (Crone and Nielsen, 1989a;
Meunier and Morin, 1989; Nielsen and Kagamihara, 1993a). This was confirmed in the present study by the observation that disynaptic reciprocal inhibition was increased and FN facilitation decreased at the onset of fast dorsiflexion movements. In the patients with spasticity, decreased FN facilitation was also seen at the onset of dorsiflexion, but there was no increase in disynaptic reciprocal inhibition. This may indicate that the failure to depress the soleus H reflex at the onset of dorsiflexion in the patients with spasticity can be explained mainly by failure to facilitate transmission in the disynaptic reciprocal inhibitory pathway.

Some time after the onset of contraction, peripheral feedback mechanisms may influence transmission in the different reflex pathways. The decrease in the H reflex and the FN facilitation towards the end of the ramp phase and during tonic dorsiflexion can thus probably be explained by a combination of central descending control and peripheral feedback mechanisms.

**Regulation in relation to plantar flexion**

The increase in the soleus H reflex during plantar flexion in healthy subjects can probably be explained to a large extent by the increased excitability of the spinal motor neurones as a consequence of the descending excitatory command. In addition, presynaptic inhibition of Ia afferents on soleus motor neurones has been shown to be decreased at the onset of plantar flexion and probably also to some extent during tonic plantar flexion (Hultborn et al., 1987b; Meunier and Pierrot-Deseilligny, 1989; Nielsen and Kagamihara, 1993a; Nielsen, 1994). Disynaptic reciprocal inhibition of the soleus motor neurones is also decreased in relation to plantar flexion (Iles, 1986; Crone et al., 1987; Nielsen and Kagamihara, 1992; Petersen et al., 1998). Disynaptic reciprocal inhibition and presynaptic inhibition of soleus Ia afferents have both been shown to be decreased at rest in patients with spasticity (Crone et al., 1994; Faist et al., 1994; Nielsen et al., 1995).

For disynaptic reciprocal inhibition, it is therefore difficult to evaluate whether a further decrease took place in relation to plantar flexion. Nevertheless, we did observe a significant decrease in inhibition at the onset of fast plantar flexion in the patients and this decrease seemed to be of the same magnitude (or even larger) in healthy subjects with a similar small reciprocal inhibition at rest as the patients with spasticity (Fig. 3B, open triangles). The control of the Ia inhibitory interneurones thus appears to be relatively intact in patients with spasticity at the onset of and during plantar flexion.

With regard to FN facilitation, we made sure that it was of a similar degree at rest in the patients and the healthy subjects. Nevertheless, a significantly smaller increase in facilitation was observed at the onset of plantar flexion in the patients. As suggested by Hultborn and colleagues, the increase in facilitation at the onset of plantar flexion in healthy subjects can be explained by removal of presynaptic inhibition from the soleus Ia afferents (Hultborn et al., 1987b). In a later study, Meunier and Pierrot-Deseilligny observed that facilitation decreased again later during the ramp phase of ramp-and-hold plantar flexion (Meunier and Pierrot-Deseilligny, 1989).

In the present study it was also observed that FN facilitation was significantly smaller towards the end of the ramp phase than at the onset of contraction. Possibly because of this, the H reflex was also decreased at this time. Meunier and Pierrot-Deseilligny argued that the removal of presynaptic inhibition around the onset of contraction and the return to the baseline level during the ramp phase was part of the descending motor programme initiating the movement (Meunier and Pierrot-Deseilligny, 1989). The failure of the patients with spasticity to increase facilitation to the same extent as the healthy subjects, and especially the lack of modulation of facilitation during movement, suggests that they are unable to use this central programme to regulate presynaptic inhibition. Iles and Roberts also provided some evidence of reduced modulation of presynaptic inhibition during tonic plantar flexion (Iles and Roberts, 1986).

When transmission in the stretch reflex pathway is compared between the healthy subjects and the patients with spasticity, it is evident that both groups have very little reciprocal inhibition and presynaptic inhibition during plantar flexion. At the same time, the α motor neurones are either at or beyond their threshold because of the descending excitatory command. It is therefore not surprising that the H reflexes are also more or less similar in size in the two groups of subjects during plantar flexion. This may also help to explain why evidence of increased muscle tone and reflex hyperexcitability is not seen during agonist contraction in patients with spasticity (Ibrahim et al., 1993; Sinkjaer and Magnussen, 1994). In healthy subjects, disynaptic reciprocal inhibition and presynaptic inhibition are decreased during contraction to the extent that is seen in patients with spasticity already at rest. It is therefore only in the resting state (and during antagonist contraction) that there is evidence of reflex hyperexcitability and increased muscle tone.

**Extensor versus flexor hypothesis**

The preserved central modulation of inhibitory pathways during soleus contraction may be explained by the relatively preserved excitation of extensor muscles that is seen in supraspinal lesions. It is well known that in man the muscle paresis caused by supraspinal lesions exhibits a typical supraspinal distribution, in which flexor muscles are more paretic than extensor (antigravity) muscles in the lower extremities and the accompanying spasticity (muscle tone and the hyperexcitable stretch reflexes) is more pronounced in these latter muscle groups (Burke, 1988).

This probably reflects a skewed net corticospinal input, in which the excitatory pathways to extensor-coupled motor neurones and interneurones are relatively spared compared with flexor-coupled neurones. Thus, it seems probable that in patients with spasticity the corticospinal pathways that modulate the reciprocal inhibitory pathways from extensor
Functional significance
The findings of the present study suggest that stretch reflex hyperexcitability in patients with spasticity probably has only limited functional significance during contraction in the agonist muscle, but that it may be a problem at rest and in relation to contraction of the antagonist muscle. Several other studies have found that signs of stretch reflex hyperexcitability that are manifest at rest disappear when the subject activates the muscle in which the stretch reflex is elicited (Ibrahim et al., 1993; Sinkjaer and Magnussen, 1994).

The likely explanation for this has been given above. If stretch reflex hyperexcitability has a functional consequence for the patients, we believe that it should be seen mainly in relation to contraction of the antagonist. Since the antagonist muscle will be stretched most quickly at the onset of contraction, this is the time that optimal prevention of unwanted stretch reflexes is most necessary. It is also at this time that reciprocal inhibition was most increased and the H reflex most depressed in healthy subjects, but not in the patients with spasticity. Several previous studies have similarly suggested that unwanted stretch reflex activity in the antagonist muscle explains some of the functional disability of patients with spasticity (Dimitrijevic and Nathan, 1967; Mizrahi and Angel, 1979; Benecke et al., 1983; Corcos et al., 1986; Boorman et al., 1996; Knutsson et al., 1997).

In the present study, the patients were able to perform the required contractions without any observable co-contraction of the antagonist muscles or any sign of stretch reflex activity in these muscles in relation to the contractions. There may be at least two reasons for this. First, all the contractions investigated were isometric and only minor changes in the length of the antagonist muscles were therefore evoked in relation to the contractions. Secondly, all the contractions had a fairly moderate speed. It seems possible that, if we had asked the patients to perform much faster contractions, unwanted activity in the antagonist muscles would have been elicited, as reported in the study by Boorman and colleagues (Boorman et al., 1996). We therefore believe that the failure to increase reciprocal inhibition, and thereby to depress stretch reflex activity in the antagonist muscle, does reflect a serious impediment for the execution of fast non-isometric movements in the patients. We propose that therapy directed at strengthening reciprocal inhibition could be useful in relieving some of the functional disability of patients with spasticity.

Acknowledgements
We wish to thank Professor Emmanuel Pierrot-Deseilligny for commenting on an early version of the manuscript and the staff at Sclerosehospitallet in Haslev, where most of the experiments were performed. The work was funded by The Danish Society of Multiple Sclerosis and the Danish Health Research Council.

References


