

# Appearance of reciprocal facilitation of ankle extensors from ankle flexors in patients with stroke or spinal cord injury

C. Crone,<sup>1</sup> L. L. Johnsen,<sup>1</sup> F. Biering-Sørensen<sup>2</sup> and J. B. Nielsen<sup>3</sup>

<sup>1</sup>Department of Clinical Neurophysiology and <sup>2</sup>Clinic for Para- and Tetraplegia, Copenhagen University Hospital and <sup>3</sup>Department of Medical Physiology, Panum Institute, University of Copenhagen, Copenhagen, Denmark

Correspondence to: C. Crone, Department of Clinical Neurophysiology, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark  
E-mail: ccrone@rh.dk

## Summary

The purpose of the present study was to investigate the pathophysiological role of reciprocal facilitation between antagonistic motoneuron pools in spasticity. The soleus H-reflex was conditioned by prior stimulation of the peroneal nerve in 15 healthy subjects, six hemiplegic patients and 11 spinal cord injured (SCI) patients. The hemiplegic patients were tested from soon after the onset of hemiplegia and up to 2 years later. Whereas stimulation of the peroneal nerve produced short-latency inhibition of the soleus H-reflex in healthy subjects, it produced facilitation in spastic

SCI and hemiplegic patients. This facilitation was demonstrated to have a low threshold compatible with activation of group I afferents and was most likely mediated by an oligosynaptic (reciprocal) excitatory pathway. The facilitation appeared in parallel with the development of hyperactive Achilles tendon reflexes, which was the only clinical finding that could be correlated positively with the facilitation. It is suggested that the appearance of reciprocal excitation plays a role in the pathophysiology of spasticity.

**Keywords:** reciprocal facilitation; H-reflex; hemiplegia; spinal cord injury; spasticity

**Abbreviations:** PN = peroneal nerve; SCI = spinal cord injured

## Introduction

Spasticity may be defined as increased resistance to passive muscle stretch and hyperactivity of tendon reflexes (Lance, 1980). The possible role of different inhibitory mechanisms in the pathophysiology of spasticity has been investigated in several studies. Much interest has been devoted to disynaptic reciprocal Ia inhibition and its supraspinal control, which in healthy subjects is responsible for depression of the activity in antagonistic muscles at the onset of and during movements (Kots and Zhukov, 1971; Tanaka, 1974; Yanagisawa *et al.*, 1976; Crone *et al.*, 1987; Crone and Nielsen, 1989, 1994; Crone, 1993; Panizza *et al.*, 1995). Transmission in this pathway has been found to be decreased at rest in spastic patients with multiple sclerosis (Crone *et al.*, 1994; Morita *et al.*, 2001) and in hemiplegic patients (Yanagisawa *et al.*, 1976; Nakashima *et al.*, 1989; Artieda *et al.*, 1991; Okuma

and Lee 1996; Crone *et al.*, 2000). Decreased reciprocal inhibition may thus be one of the pathophysiological mechanisms in spasticity, but none of these studies have been able to demonstrate a correlation between the decrease of reciprocal inhibition and the severity of spasticity. This suggests that other mechanisms must be involved.

Myklebust and colleagues described reciprocal excitation of antagonistic muscles in children with cerebral palsy and argued that this was due to a 'developmental error', since a similar excitation was not found in normal children or in patients with adult-onset spasticity (Myklebust *et al.*, 1982). However, there are occasional reports in the literature of reciprocal facilitation between antagonistic muscles in patients with adult onset spasticity (Yanagisawa *et al.*, 1976; Yanagisawa, 1980; Crone *et al.*, 1994; Okuma *et al.*, 2002) or with decreased glycinergic inhibition (Crone *et al.*,

2001). This raises the possibility that reciprocal excitation also plays a role in the pathophysiology of adult-onset spasticity. The purpose of this study was to investigate this possibility.

## Patients

Eleven patients with spinal cord injury (SCI) and six hemiplegic patients from the Department of Neurology at Rigshospitalet (University Hospital of Copenhagen) were included in the study. In addition, one patient who had an infarct located to the brainstem was included.

The SCI patients (eight male and three female) were between 27 and 59 years of age (mean 38.5 years old). Ten patients were paraplegic/tetraplegic due to trauma and one patient due to syringomyelia. The spinal lesions were located between the second cervical segment (C2) and the eighth thoracic segment of the spinal cord (Th8). The onset of the event leading to SCI had taken place between 6 months and 16 years ago (mean duration 7.7 years). Seven patients had a complete SCI, while four patients had an incomplete SCI. The SCI patients were tested once.

The hemiplegic patients (three males and three females) were between 54 and 79 years of age (mean 68 years old). Five of the patients had suffered a cerebral infarction and one patient a cerebral haemorrhage. CT scans of the brain had been performed in all patients after onset of the present disease and only patients without signs of previous cerebral strokes or structural brain damage (other than that explained by the present disease) were included in the study. None of the patients had a history of previous neurological disease (no previous sensory disturbances, loss of power, gait disturbances or speaking difficulties). Five of the hemiplegic patients were included in the study as soon after onset of symptoms as their general condition allowed and three underwent several electrophysiological tests during the development of the symptoms (between five and eight testing sessions with an interval of 2–8 weeks plus, in two patients, a control test one year and two years later). Two patients went through one test only. One patient was included in the study after he had reached a more chronic stage (4.5 months after onset of disease). This patient was tested twice.

The patient with the brainstem infarct had been tested several times in our laboratory prior to the onset of the disease as part of our group of healthy control subjects (Crone *et al.*, 1994). The onset of the disease was 4 years ago when the patient was 68 years old. The location of the infarct was determined by MRI. The infarct caused tetraplegia, speech impairment and swallowing difficulties in the acute phase. Almost normal muscle strength was regained on the right side within 14 days after the infarct, while muscle power on the left side slowly improved over the next 6 months. At the time of the present test, the patient had normal muscle power on the right side, but some power loss [force 4+ according to the Medical Research Council (MRC) rating scale] for ankle dorsiflexion and increased fatigability in the left leg (i.e. the

patient had difficulties maintaining maximal ankle dorsiflexion for >5 s and experienced foot drop after <500 m walk). Patellar and Achilles reflexes were hyperactive bilaterally, but ankle clonus could not be elicited on either side. Muscle tone was normal in both arms and legs. Prior to the onset of disease, the patient had not suffered from any neurological disorders.

## Methods

### *Clinical neurological testing*

The same person tested all the hemiplegic patients clinically at all sessions. Two different examiners tested the SCI patients. Walking ability was judged and the muscle strength for ankle dorsi- and plantar flexion, knee flexion and extension was tested. Patellar, Achilles and plantar reflexes and ankle clonus were evaluated according to the MRC rating scale. Ankle clonus and muscle tone in the legs were evaluated using the Ashworth scale (Ashworth, 1964). The patients were asked if they had experienced muscle spasms or other involuntary leg movements. The clinical findings can be seen in Table 1.

The 15 healthy subjects (10 male and five female) were between 23 and 65 years of age (mean 34 years old). None of the subjects had any history of neurological disease.

All healthy subjects and all patients were given oral and written information about the investigation, which had been approved by the local ethical committee of Copenhagen and Frederiksberg. All experiments were performed according to the Declaration of Helsinki.

### *H-reflex*

The subjects were seated in an armchair with the examined leg semi-flexed in the hip (120°), the knee flexed to 160° and the ankle in 110° plantar flexion. The foot was attached to a foot plate, which was connected to a torque meter. Surface electrodes were used for both stimulation and recording EMG activity. The experiments were performed at rest. The soleus H-reflex was evoked by stimulating the tibial nerve through a monopolar stimulating electrode (1 ms rectangular pulse) in the popliteal fossa. The reflex responses were measured as the peak-to-peak amplitude of the non-rectified reflex. The reflexes were recorded by disc electrodes (silver–silver chloride electrodes, 1 cm<sup>2</sup> recording area, 2 cm between the poles) placed over the soleus muscle. The size of the control H-reflex was adjusted to 20–25% of  $M_{max}$  in all situations (Crone *et al.*, 1990). Control and conditioned reflexes (see below) were randomly alternated at 4 s intervals. The data were stored on a computer for subsequent statistical analysis.

### *Conditioning stimulation of the peroneal nerve*

The H-reflex was conditioned by stimulation of the peroneal nerve (PN) (rectangular 1 ms pulse) by bipolar surface

electrodes placed 1–3 cm distal to the neck of the fibula. Specific care was taken to ensure that the conditioning stimulus was applied at a position where the threshold for the M-response in the tibialis anterior muscle was lower than the threshold for the M-response in the peroneal muscles. The specificity of this stimulation was checked repeatedly during the experiments. The conditioning stimulus strength was expressed in multiples of the M-threshold ( $\times$  MT) in the tibialis anterior muscle and was kept at  $1.0 \times$  MT. In all subjects, a time course of the effect of PN stimulation (stimulation strength  $1.0 \times$  MT) on the soleus H-reflex was investigated at rest. Conditioning test intervals from 1 to 10 ms in 1 ms steps were investigated in all subjects. In some subjects, additional conditioning test intervals up to 40 ms were investigated. At least 20 control and 20 conditioned reflexes (at each conditioning-test interval) were sampled at each testing session. In three of the six hemiplegic patients, this test was performed in both legs.

### Data analysis

The mean and standard error of the mean were calculated for all measurements online. Differences in the size of the conditioned and control reflexes were tested using Student's *t*-test. Spearman rank size was used to test for a possible correlation between the clinical manifestations and the amount of reciprocal facilitation/inhibition.

## Results

### The effect of PN stimulation on the soleus H-reflex in hemiplegic and SCI patients

Figure 1 shows the population mean of the effect of conditioning PN stimulation on the soleus H-reflex in 15 healthy subjects (Fig. 1A), in six hemiplegic patients (tested 2–30 weeks after onset of the cerebrovascular disease, Fig. 1B) and in 11 SCI patients (tested 6 months–16 years after onset of paraplegia, Fig. 1C). In the healthy subjects, the PN stimulation evoked an inhibition of the soleus H-reflex at a conditioning-test interval of 2–4 ms. This short latency inhibition has been demonstrated to be caused by activation of the disynaptic reciprocal Ia inhibitory pathway (Crone *et al.*, 1987; Crone and Nielsen, 1989, 1994) projecting from the peroneal nerve to soleus motoneurons. At conditioning test intervals  $>5$  ms, a second period of inhibition was observed. This inhibition has been named D1 (Mizuno *et al.*, 1971) and is generally accepted to be caused by presynaptic inhibition of soleus Ia afferents.

There is a considerable variability in the amount of the early inhibition among healthy subjects, but it is seen in nearly all subjects and the inhibition is increased at the onset of dynamic ankle dorsi-flexion in all healthy subjects (Crone and Nielsen, 1989; Crone *et al.*, 1994). In the present material, the average depression of the H-reflex at a conditioning test interval of 2 ms was 13% (i.e. the

conditioned reflex depressed to 87% of its control size) in the healthy subjects. In 11 of the subjects, there was a statistically significant depression ranging from 10% to 40%.

In none of the six hemiplegic or 11 SCI patients was an early inhibition observed. The pooled data from these patients demonstrate this lack of inhibition (Fig. 1B and C). Instead, a facilitation was observed on the paretic side of the hemiplegic patients (Fig. 1B, filled circles) and in the SCI patients (Fig. 1C). The facilitation had an onset at conditioning test intervals of  $\sim 2$ –3 ms and lasted 10–12 ms (the last part of the facilitation is not shown in Fig. 1B).

Figure 2 shows data from all individual hemiplegic patients. It is seen that the facilitation was present in all patients on the paretic side (Fig. 2, filled circles), but never on the non-paretic side (Fig. 2, open circles).

The facilitation was seen in six of the 11 SCI patients, and was generally somewhat smaller and of shorter duration in these patients than in the hemiplegic patients. The facilitation was seen in two of the four patients with a partial lesion of the spinal cord and in four of the seven subjects with a complete lesion.

The mean  $H_{\max}/M_{\max}$  ratio in the SCI patients in whom a facilitation was seen was significantly larger than in the patients without a facilitation (mean  $\pm$  standard deviation:  $69.2 \pm 23.6\%$  and  $29.6 \pm 24.0\%$  for the patients with and without facilitation, respectively;  $P < 0.05$ ). When pooling data from both SCI and hemiplegic patients, a clear positive correlation was found between the size of the facilitation and the size of the  $H_{\max}/M_{\max}$  ratio (Spearman rank  $P < 0.01$ ; correlation coefficient: 0.4; Fig. 3).

The described facilitation was not observed in any of the 15 healthy subjects included in this study. Furthermore, we have tested  $>100$  healthy subjects in our laboratory during the past 15 years and have never observed a similar facilitation either at rest or during voluntary movement, when the conditioning stimulation was selective to the branch innervating the tibialis anterior muscle (C. Crone and J. B. Nielsen, personal observation).

It should be noted that it appears from Fig. 1 as if the D1 inhibition is absent in the hemiplegic and SCI patients (compare conditioning test intervals between 6 and 10 ms in Fig. 1A–C). However, this is due to the facilitation observed in the patients. At longer intervals, as seen from Fig. 2, the D1 inhibition was of a similar size in the hemiplegic patients as in the healthy subjects. D1 at these long intervals was not measured in the SCI patients.

Figure 4 demonstrates data from one subject in whom measurements were made before and after stroke. The patient was originally tested in 1987 (Fig. 4A), when he participated as a healthy control subject for another study (Crone *et al.*, 1994). At this time, he had a clear disynaptic reciprocal inhibition of the soleus H-reflex on the right side. Reciprocal inhibition of a similar magnitude was measured again shortly before he had an infarct in the brainstem in 1998 (but an elaborate time course was not obtained at that time). Immediately after the infarct the patient was tetraplegic. He

**Table 1** Clinical neurological testing

Patient	Age	Diagnosis	Time after onset of disease	Ankle dorsiflexion force	Ankle plantarflexion force	Muscle tone (knee-joint)	Muscle tone (ankle-joint)	Patellar reflex: left/right	Achilles reflex: left/right	Ankle clonus	Plantar reflex on affected side	Muscle spasms (paretic leg)
Hemiplegic patients	GP	74	Bleeding right cerebral hemisphere	0	0	Slightly decreased	Slightly decreased	++/+++	+++	No	No response	0
				1	1	Slightly decreased	slightly decreased	+++	+++	Yes	No response	Few
				3	4	1	1	+++	+++	Yes	No response	None
	LL	60	Infarct right cerebral hemisphere	3	4	1	1	++	+++	No	Babinski	None
OH				4	4+	1	1	++	+++	No	Babinski	None
				4+	5-	1	1	+++	+++	No	Normal	None
				5-	5	1	1	+/0	+/0	No	Normal	None
				4	4	1	1	+/+++	0/++	3 extra beats	Normal	None
KA				4	4+	2	2	0/+++	0/+++	4-5 extra beats	Extensive	Yes, regularly
				4+	4+	2	2	++	+++	5-6 extra beats	Extensive	Yes, regularly
				5-	5-	3	3	++	+/+	No	Atypical	Very rare
77	Several infarcts right hemisphere	4 months	3	3-4	3	3	+++	+++	Yes	Babinski	No spasms, but stiffness	
VL	79	Infarct left hemisphere	4 weeks	5-	5	1	1	++	+++	No	Atypical	None
IJ	54	Infarct right hemisphere	2 weeks	4+	4+	1	1	+++	+++	Yes	Babinski	None
SCI patients	JB (F)	22	Traumatic C2 Partial	5	4	1	2	++	+++	Yes	No response	None
	PE	59	Traumatic C1-C2 Partial	3-4	3-4	1	1	++	+++	No	Babinski	None
JR (F)	55	Traumatic C6-C7 Complete	0	0	2	2	++	+++	Yes	Normal	Normal	Many

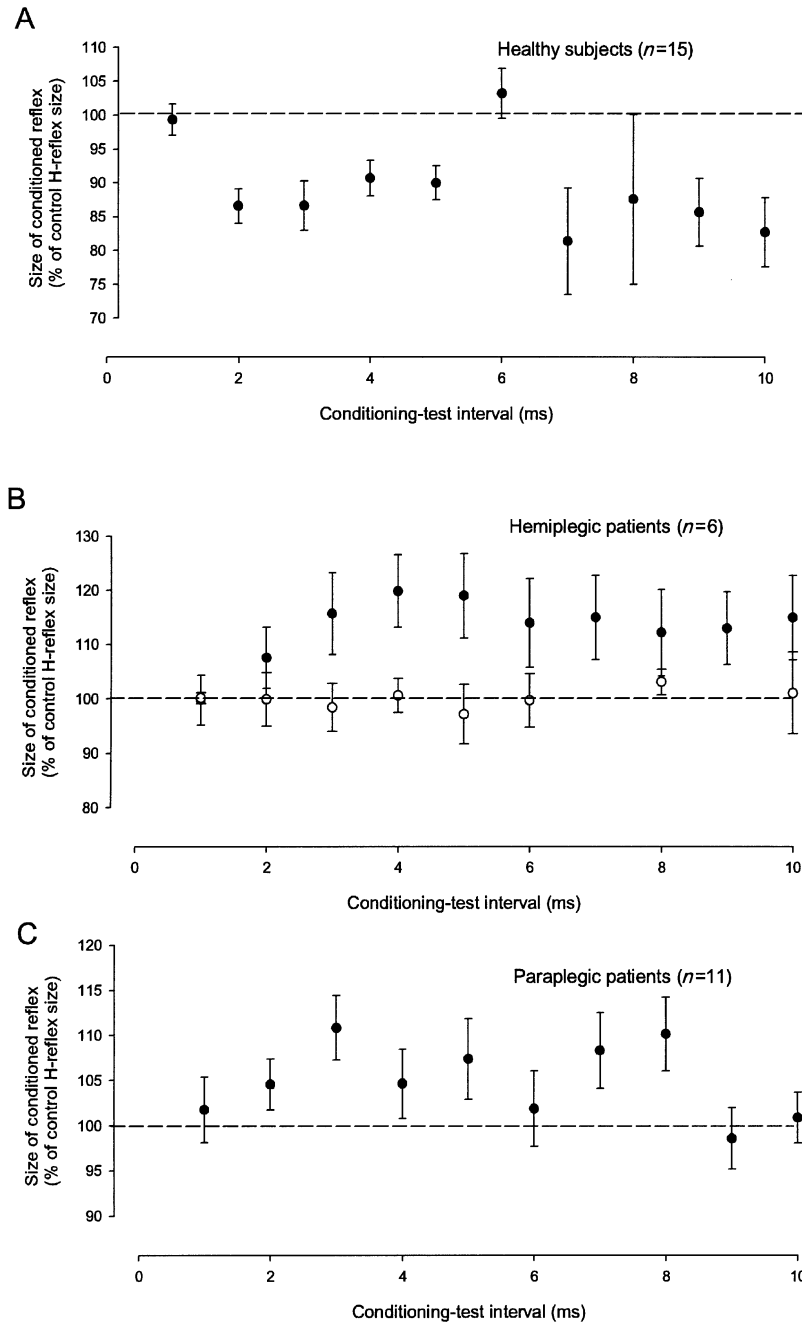
**Table 1** *Continued*

Patient	Age	Diagnosis	Time after onset of disease	Ankle dorsiflexion force	Ankle plantarflexion force	Muscle tone (knee-joint)	Muscle tone (ankle-joint)	Patellar reflex: left/right	Achilles reflex: left/right	Ankle clonus	Plantar reflex on affected side	Muscle spasms (paretic leg)
LSE	57	Traumatic C5-C6 Complete	15 years	0	0	3	3	+/+	+++/>+++	Yes	No response	Many
JW (F)	28	Traumatic C5 Complete	4 years	0	0	2	2	+++/>+++	+++/>+++	No	No response	Many
KM (F)	54	Traumatic C2 Complete	7 years	0	0	1	1	+/>+	+/>+	No	No response	Many
JDP (F)	34	Traumatic C6 Complete	8 years	0	0	3	3	+/>+	+++/>+++	Yes	Babinski	Some
HN	27	Traumatic Th4 Complete	9 years	0	0	2	2	+/>+	+/>+	No	No response	Some
ILAD	53	Traumatic Th4 Complete	4 years	0	0	2	2	+/>+	+++/>+++	Yes	No response	Many
MR (F)	45	Syringomyelia Th8 Partial	2 years	3	4	2	2	+++/>+++	+++/>+++	No	No response	Many
LCR	42	Traumatic C5-C6 Partial	5 years	2	3	3	3	+++/>+++	+++/>+++	Yes	Babinski	None

Only findings from the paretic limb in the hemiplegic patients are shown, except the reflex evaluation, which is shown for both sides. The muscle power was evaluated according to the MRC rating scale; 5 = normal power; 4 = active movement against gravity and resistance; 3 = active movement against gravity; 2 = active movement with gravity eliminated; 1 = trace of contraction; 0 = no contraction. Muscle tone was evaluated according to the Ashworth scale: 1 = no increase in tone; 2 = slight increase in muscle tone and 'catch' during passive movement; 3 = more marked increase in muscle tone, but the limb is easily moved; 4 = considerable increase in tone, passive movement difficult; 5 = affected part(s) is rigid in flexion or extension. Tendon reflexes were graded as: 0 = absent, + = hypoactive, ++ = normal, +++ = hyperactive. (F) after the initials of the patients indicates that a facilitation of the soleus H-reflex following PN stimulation was found.

recovered full strength on the right side, while some power loss remained on the left side (see Methods for more details). At the time of testing (in year 2002) Achilles and patellar

reflexes were hyperactive bilaterally and on the left side ankle dorsiflexion force was diminished (force 4+), while it was normal on the right side. As seen in Fig. 4B disynaptic



**Fig. 1** The time course (at rest) of the effect of a conditioning peroneal nerve stimulation (single 1 ms stimuli applied to the peroneal nerve 2–3 cm distal to the caput fibulae, stimulation strength of  $1.0 \times MT$ ) on the size of the soleus test H-reflex. (This was evoked by single 1 ms stimuli applied to the tibial nerve in the popliteal fossa. Size of the unconditioned soleus H-reflex 20–25% of  $M_{max}$ .) The abscissa shows the interval in ms between the conditioning stimulus and the test stimulus. The ordinate shows the size of the conditioned test reflex expressed in percentage of the test reflex. In (A), the mean of the results from 15 healthy subjects are seen. The mean results from six hemiplegic patients (described in Table 1, hemiplegic patients) are shown in (B) and the mean results from 11 SCI patients (described in Table 1, SCI patients) with spinal cord lesions between C2 and Th8 are seen in (C). The open circles in (B) are from the non-paretic side, whereas the filled circles are from the paretic side. The vertical bars indicate the standard error of the mean.

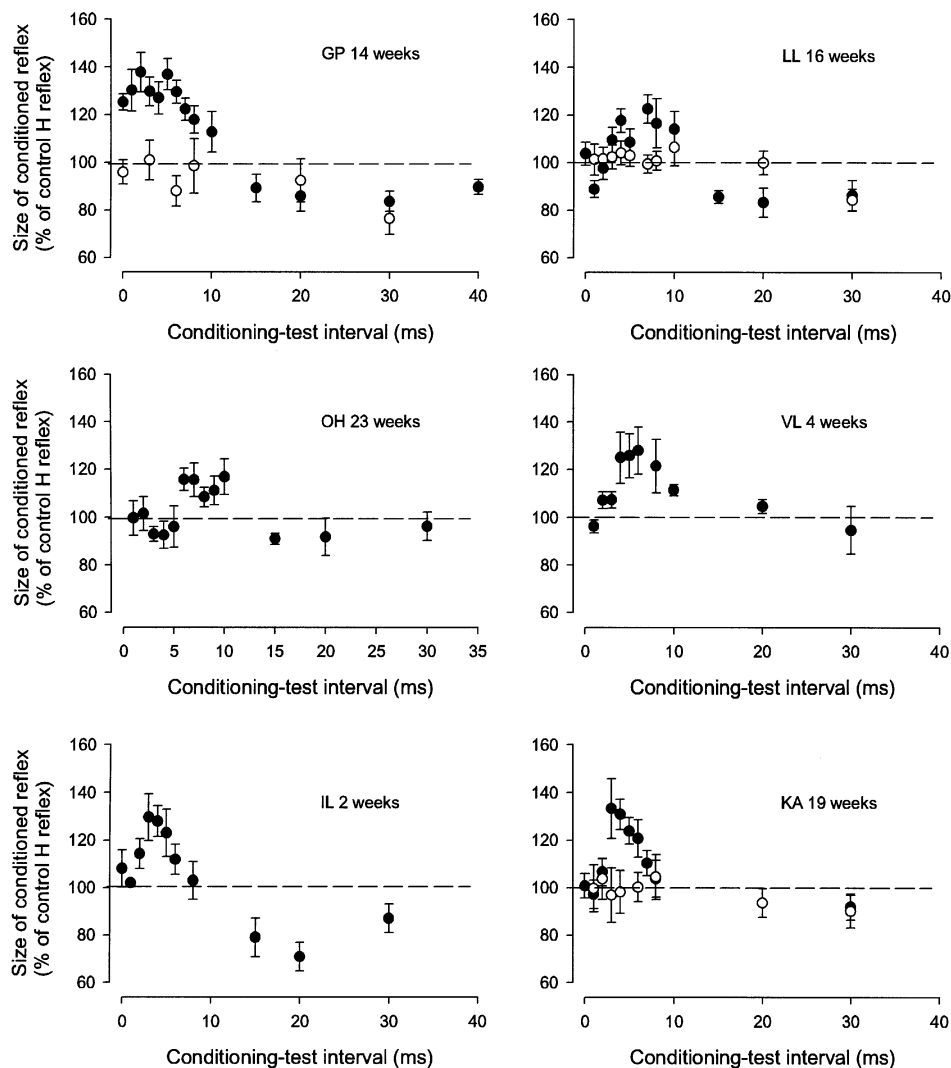
reciprocal inhibition was not present on either side and on the left (most affected) side a facilitation was seen at a conditioning-test interval of 6–8 ms.

**Changes in the effect of PN stimulation on the soleus H-reflex following onset of hemiplegia**

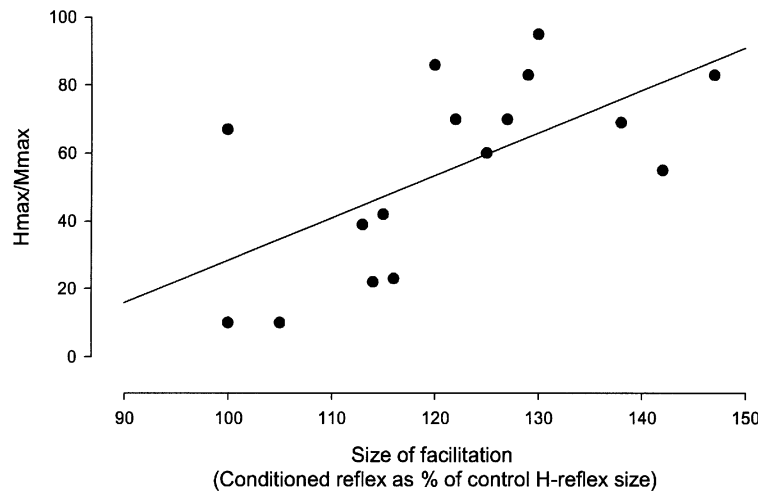
In order to investigate changes in the effect of the PN stimulation on the soleus H-reflex at different times after the primary lesion, repeated measurements were made for up to 2 years in the hemiplegic patients.

Figure 5 shows data from a 74-year old patient (GP), who suffered an intracerebral haemorrhage in the right cerebral hemisphere. At the onset of the disease, she was paralytic in the left leg and arm. Her general condition did not allow electrophysiological testing until 3 weeks after onset of disease, where PN stimulation produced a small inhibition at

a conditioning test interval of 20–30 ms in both legs (D1 inhibition), but no short latency inhibition on either side. At this time, the patient had no ankle clonus and no spasms in the left paralytic leg, and Achilles and patellar reflexes were normal and equal. Muscle tone in the left leg was slightly decreased (see Table 1, hemiplegic patients). At the next testing occasion 2 weeks later (Fig. 5B and Table 1, hemiplegic patients), a clear increase in the ankle and patellar reflexes were seen on the paretic side, ankle clonus had developed and the patient started to complain of muscle spasms. Tendon reflexes in the right leg were unchanged and normal. At this second testing and on the following occasions up to 30 weeks after the cerebrovascular insult, PN stimulation produced a clear facilitation of the soleus H-reflex at a short conditioning test interval of 1–10 ms on the paretic side (Fig. 5B and C, filled circles), while no early facilitation or inhibition was seen on the unaffected side (Fig. 5B and C,



**Fig. 2** Time course of the effect of peroneal stimulation on the soleus H-reflex in each of the six hemiplegic patients. Filled circles show data from the paretic side and open circles data from the non-paretic side. Other details as for Fig. 1.



**Fig. 3** Correlation between size of the soleus  $H_{\max}/M_{\max}$  ratio and the size of reciprocal facilitation in five hemiplegic and 11 SCI patients. Each point represents one subject. The abscissa shows the maximal facilitation of the soleus H-reflex evoked by a conditioning stimulation of the peroneal nerve at a conditioning test interval of 4–7 ms. The facilitation is expressed as a percentage of the unconditioned value of a control H-reflex size. The  $H_{\max}$  and the  $M_{\max}$  values were measured at the start of the experiment. For patients who were tested several times, the results from the last measurement is shown.  $R^2$  was 0.4.

open circles). The patient slowly regained some force in the left leg (up to force 4 in the left leg), but otherwise the clinical findings stayed unchanged throughout this observation and testing period of 7 months (see Table 1, hemiplegic patients). In the remaining five patients, a short latency facilitation was either seen the first time the patients were tested (as early as 2 weeks after onset of disease) or it developed to become stable and pronounced along with the development of hyperactive Achilles reflexes. A pronounced facilitation was never seen in hemiplegic patients who did not at some stage have hyperactive Achilles tendon reflexes. In two hemiplegic patients, the hyperactivity of the ankle jerk disappeared, but a reflex asymmetry remained (with a relative hyperactivity on the paretic side).

The development of the facilitation did not correlate with changes in tonus in the leg, muscle spasms, walking speed/ability or abnormalities/side differences in patellar reflexes.

### ***Which pathway mediates the facilitation of the soleus H-reflex produced by PN stimulation in hemiplegic patients?***

In order to investigate which spinal pathways mediate the described short latency facilitation, the conditioning stimulus strength was graded in four patients at a short conditioning test interval (5 or 6 ms) and in two patients also at a conditioning test interval of 20 ms (data not shown). It is seen from Fig. 6 that the facilitation in every patient had an onset at a weak conditioning stimulus strength around  $0.8 \times MT$ .

## **Discussion**

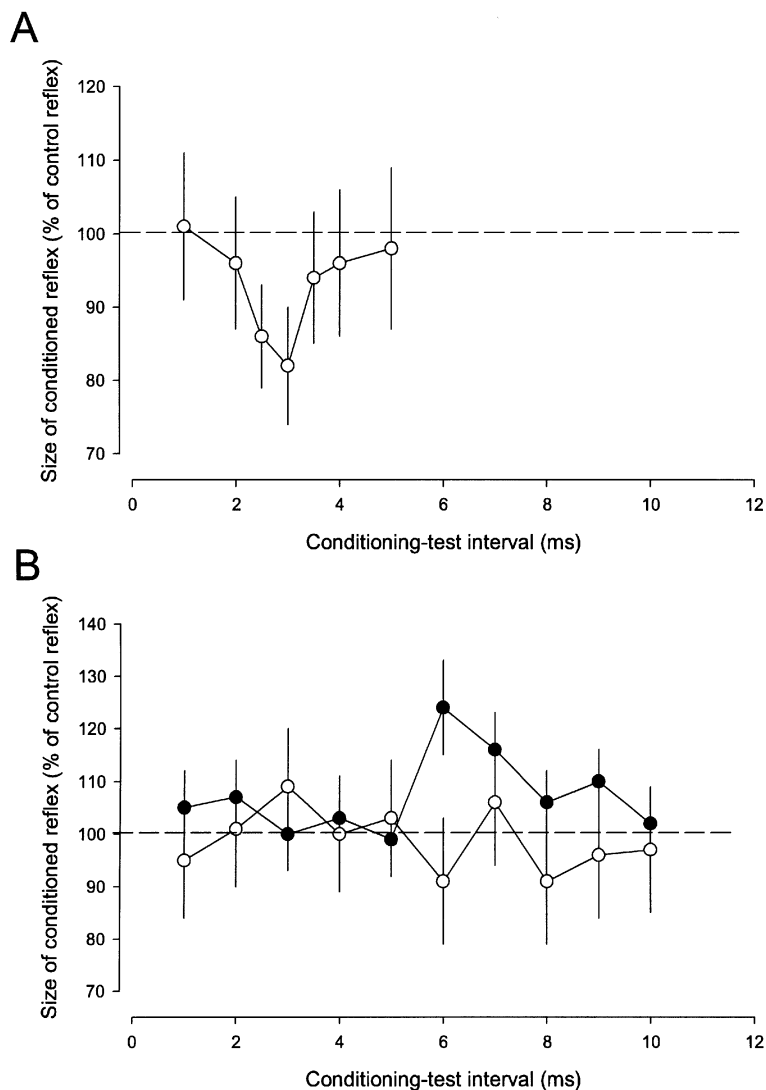
The main findings in the present study are that early reciprocal inhibition is replaced by a short latency reciprocal facilitation of soleus H-reflexes in both SCI and hemiplegic patients, and that the size of the facilitation correlated positively with increased reflex activity of the ankle plantar flexors. Furthermore, the facilitation appeared at the same time as Achilles reflex hyperactivity developed on the paretic side in the hemiplegic patients. In one patient, measurements were obtained before and after a brain stem infarct. In this patient, reciprocal inhibition disappeared after the infarct and a facilitation appeared on the most affected side.

Myklebust and colleagues observed reciprocal excitation in children with cerebral palsy, but not in patients with adult-onset spasticity and normal healthy subjects, and therefore argued that the reciprocal excitation was due to a ‘developmental error’ caused by the disease (Myklebust *et al.*, 1982). The observation in the present study as well as occasional reports in previous studies (Yanagisawa *et al.*, 1976; Crone *et al.*, 1994, 2001; Okuma *et al.*, 2002) of reciprocal facilitation in patients with paraplegia as well as hemiplegia suggest that reciprocal facilitation is also a common feature of adult-onset spasticity.

### ***Which pathway is responsible for the facilitation?***

Ia afferents from the peroneal muscles have been shown to produce a monosynaptic excitation of soleus motoneurons (Meunier *et al.*, 1993). One possibility is therefore that the facilitation was caused by activation of the peroneal nerve





**Fig. 4** Time course of the effect of PN stimulation on the soleus H-reflex in a single subject before (A) and after (B) an infarct in the brainstem. Measurements from the right leg are shown as open circles, whereas measurements from the left leg are shown as filled circles. The measurements in (A) were obtained in 1987, whereas the measurements in (B) were obtained in 2002. Other details as for Fig. 1.

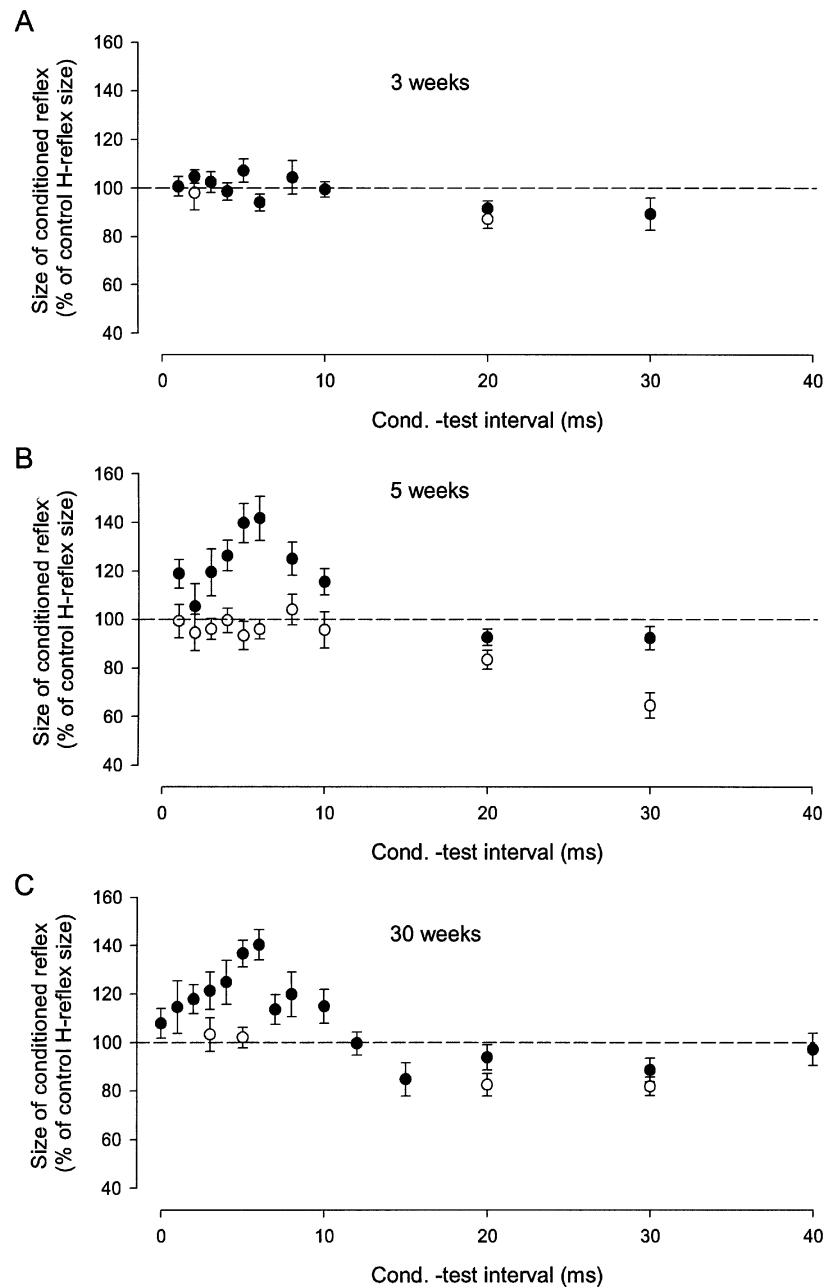
branch in the patients. However, care was taken to stimulate only the branch to the tibialis anterior muscle in both patients and healthy subjects (see Methods). We have occasionally observed a slight short latency facilitation in healthy subjects when the conditioning PN stimulation was not sufficiently selective. However, the facilitation has never been seen in the >100 normal subjects we have tested in this laboratory, when the conditioning stimulation electrode was placed so that the M-response in the tibialis anterior muscle had a lower threshold than the M-response in the peroneal muscles. The facilitation has not been described in other published investigations in healthy subjects and, in the present investigation, it was never demonstrated on the healthy side in hemiplegic patients. It could be argued that presynaptic inhibition of Ia afferents is diminished in spastic patients

(Faist *et al.*, 1994; Nielsen *et al.*, 1995) and that this would cause the monosynaptic excitation from the peroneal muscles to be revealed only in the spastic patients. However, Faist and colleagues only observed reduced presynaptic inhibition in SCI patients (Faist *et al.*, 1994), whereas it was normal in hemiplegic patients. The observation of a D1 inhibition in the hemiplegic patients in the present study also indicates that presynaptic inhibition was at least relatively intact in these patients. Furthermore, the facilitation may also be observed in patients with hereditary startle disease, who have intact presynaptic inhibition (Crone *et al.*, 2001).

The threshold of the facilitation was found to be around  $0.8 \times MT$  (Fig. 4), which is similar to the threshold for a presumed group Ib mediated inhibition of the soleus H-reflex following stimulation of the medial gastrocnemius motor

nerve (Pierrot-Deseilligny *et al.*, 1979, 1981). Effects induced by group Ia afferents generally have a threshold around  $0.6\text{--}0.7 \times \text{MT}$  (Crone *et al.*, 1987), whereas effects mediated by

group II afferent fibres have a threshold around motor threshold (Simonetta-Moreau *et al.*, 1999). The latency of the onset of the facilitation (conditioning test intervals of 2–3 ms)



**Fig. 5** The time course of the effect of peroneal nerve stimulation on the soleus H-reflex in a hemiplegic patient (GP) at different times after the cerebrovascular insult. The effect of PN stimulation on the soleus H-reflex was investigated at eight different times altogether after the insult. The results from three of these testing occasions (3, 5 and 30 weeks) are shown in A–C. The conditioning stimulus was a single 1 ms stimuli applied to the peroneal nerve 2–3 cm distal to the caput fibulae, stimulation strength of  $1.0 \times \text{MT}$ . The soleus test H-reflex was evoked by single 1 ms stimuli applied to the tibial nerve in fossa poplitea and the size of the unconditioned soleus H-reflex was  $20\text{--}25\%$  of  $M_{\text{max}}$ . The ordinate in each of the graphs is the size of the conditioned H-reflex expressed as a percentage of the control soleus H-reflex size. The abscissa is the conditioning-test interval between the PN stimulation and the stimulation of the tibial nerve, which elicited the H-reflex. The filled circles represent measurements from the paretic leg and the open circles measurements from the non-paretic leg. The vertical bars show the standard error of the mean.

is consistent with a disynaptic effect.

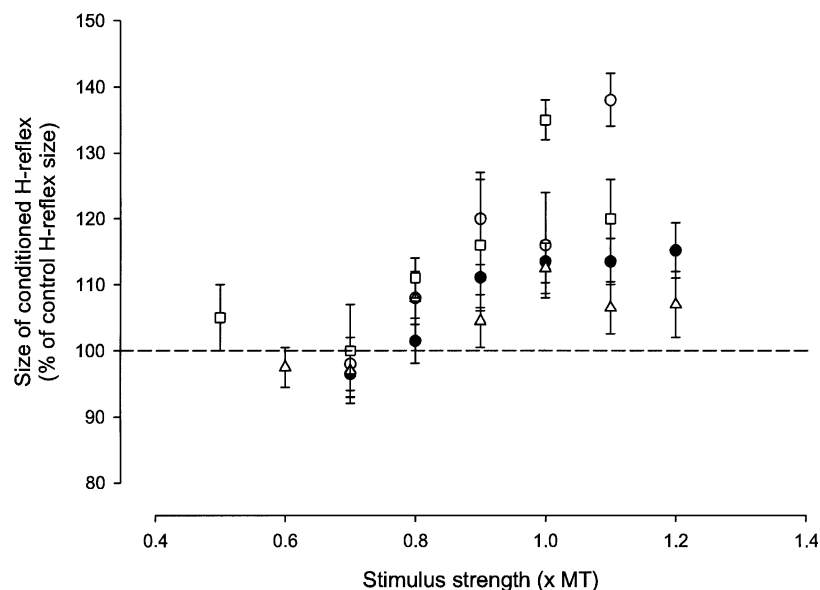
These findings suggest that the facilitation may be caused by activation of a pathway similar to the disynaptic Ib facilitatory pathway, which has been described in cat (Laporte and Lloyd 1952; Eccles *et al.*, 1957*a, b*). Later studies have demonstrated that the 'group Ib' interneurons also receive a significant input from group Ia afferents and the pathway is therefore probably more correctly described as a group I reciprocal facilitatory pathway (Jankowska, 2001).

### Which mechanism is responsible for the appearance of the facilitation in spastic patients?

A similar reciprocal disynaptic facilitation in the cat was described by Bradley and colleagues (Bradley *et al.*, 1953) when transmission in the glycinergic reciprocal Ia inhibitory pathway was blocked by strychnine. Since decreased transmission in the disynaptic Ia reciprocal pathway has been documented in all the subjects in whom the facilitation has been observed, it could be argued that the reciprocal group I facilitation is normally 'overridden' by a strong disynaptic reciprocal inhibition and that the facilitation becomes visible only once the inhibition has disappeared. Although this possibility cannot be fully excluded there are several arguments why we find it unlikely. First, a short latency facilitation has never been observed in the normal subjects in whom no or very little disynaptic reciprocal inhibition can be

demonstrated. Secondly, in the hemiplegic patients, it was never observed on the non-paretic side where the disynaptic reciprocal inhibition was also absent. Thirdly, in the patient who suffered from a brainstem infarct, reciprocal inhibition was measured on the right side before the onset of the disease. However, after the infarct the reciprocal inhibition had disappeared, but a facilitation was only seen on the left side where residual power loss and increased fatigability was present [the patient had no power loss (or complaints) on the right side]. Fourthly, a reciprocal facilitation has never been seen during plantarflexion of the ankle during which the disynaptic reciprocal inhibition decreases considerably or disappears. Nor has it been observed during co-contraction of ankle extensor and flexor muscles, where a reciprocal facilitatory function could seem appropriate (Nielsen and Kagamihara, 1992). Finally, it is never seen in healthy subjects when grading the conditioning stimulus strength at a conditioning-test interval where the disynaptic reciprocal inhibition has started to diminish and where one would expect a group I mediated facilitation (with a slightly longer latency) to appear (C. Crone and J.B. Nielsen, personal observation).

It is also unlikely that the structures mediating the facilitation are generated *de novo* after onset of disease and it must therefore be presumed that the pathway structurally exists in healthy subjects. A more likely possibility is then that the activity in the pathway is normally strongly inhibited by supraspinal inhibitory pathways, which have been disrupted in the patients. The appearance of the facilitation



**Fig. 6** The size of the conditioned soleus H-reflex and its change with different stimulation strengths of the conditioning stimulus. The abscissa shows the strength of the conditioning peroneal nerve stimulation expressed in multiples of the threshold of the tibialis anterior EMG activity (MT). The ordinate shows the size of the conditioned H-reflex expressed as a percentage of the control soleus H-reflex size. The results from four different patients are shown. The conditioning test interval was 5 or 6 ms. The vertical bars designate the standard error of the mean.

might therefore be regarded as a 'release phenomenon' as suggested by Yanagisawa (1980). However, it has to be stressed that the facilitation did not appear immediately after the lesion in at least the hemiplegic patient in whom a measurement was obtained shortly after onset of the disease, but only after some weeks. It may therefore be a result of an adaptation of the transmission in the spinal pathway after disruption of the supraspinal control.

A lack of disynaptic reciprocal inhibition has previously been suggested to play a causal role in the development of spasticity (Yanagisawa *et al.*, 1976; Nakashima *et al.*, 1989; Artieda *et al.*, 1991; Crone *et al.*, 1994, 2000; Okuma and Lee 1996; Morita *et al.*, 2001). The age and the small number of the hemiplegic patients make it difficult to use the observation of absent reciprocal inhibition on the non-spastic side in three patients as an argument against this hypothesis. The data from the patient with a brainstem infarct are unique, since measurements were obtained before and after the infarct. These demonstrated a clear reciprocal inhibition before, but not 4 years after the infarct. There is a possibility that this disappearance of reciprocal inhibition was caused by the increased age of the subject, but measurements of reciprocal inhibition were made twice with similar results 11 years apart prior to the infarction. It therefore seems most likely that the disappearance of reciprocal inhibition was caused by the infarct.

### ***Does the reciprocal facilitation play a role in the pathophysiology of spasticity?***

Due to the limited number of patients who were willing to participate in several testing sessions, it is difficult to draw any firm conclusions regarding the causal relationship between changes in the reciprocal pathways and the development of spasticity. However, the only clinical sign that could be correlated with the reciprocal facilitation was the development of absolute or relative hyperactivity of Achilles tendon reflexes: when a stable facilitation on the hemiparetic side was found ankle jerks had become hyperactive ( $\pm$  ankle clonus) on that side, while they remained normal or weak on the healthy side. Furthermore, patients in whom the facilitation was observed had significantly larger soleus H-reflexes than patients in whom no facilitation was observed. It thus seems likely that the reciprocal facilitation plays a causal role for the development of hyperactivity in the stretch reflex pathway and that it thereby may contribute to the development of spasticity. This may be supported by a previously published study by Delwaide and Olivier (1988), although a different neural pathway was investigated. They observed that Ib inhibition between the medial gastrocnemius and soleus muscles in six hemiplegic patients was replaced by a pronounced Ib facilitation on the hemiparetic, but not the unaffected side. A positive correlation was found between the facilitation and the degree of spasticity as assessed by the Ashworth scale. However, Downes and colleagues (Downes

*et al.*, 1995) found that Ib inhibition was preserved in paraplegic patients and suggested that alteration of transmission in the Ib pathways may depend on the site of the original lesion. The reason for the discrepancy between our findings in SCI subjects and the findings by Downes and colleagues (Downes *et al.*, 1995) is unclear, but may reflect that different pathways were investigated.

The correlation between the reciprocal facilitation described in the present study and the development of hyperactive tendon reflexes must be confirmed in a larger number of patients but, so far, it seems likely that the facilitation contributes to the exaggerated stretch reflexes, which are part of the clinical syndrome of spasticity. It also seems likely that the reciprocal facilitation may contribute to adverse co-contraction of antagonistic muscles during voluntary movement in spastic patients. However, the pathophysiology of spasticity is still far from clarified and it seems most likely that spasticity is a complex symptom where several different neuronal mechanisms contribute to a variable extent in individual subjects and/or different groups of patients. In the present study, we have emphasized a potential role of reciprocal facilitation, but other mechanisms such as decreased reciprocal inhibition or decreased pre-synaptic inhibition undoubtedly also play a role.

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