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Reciprocal inhibition and corticospinal transmission in the arm and leg in patients with autosomal dominant pure spastic paraparesis (ADPSP)

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Summary

The pathophysiological mechanisms underlying the development of spasticity are not clear, but the excitability of the disynaptic reciprocal inhibitory pathway is affected in many patients with spasticity of different origin. Patients with genetically identified autosomal dominant pure spastic paraparesis (ADPSP) develop spasticity and paresis in the legs, but usually have no symptoms in the arms. Comparison of the spinal and supraspinal control of the legs and arms in these patients may therefore provide valuable information about the pathophysiology of spasticity. In the present study, we tested the hypothesis that one of the pathophysiological mechanisms of spasticity in these patients is abnormal corticospinal transmission and that this may lead to decreased reciprocal inhibition. Ten patients and 15 healthy age-matched control subjects were investigated. The patients were all spastic in the legs (with hyperactive tendon reflexes, increased muscle tone and Babinski sign), but had no neurological symptoms in the arms (except for one patient). Disynaptic reciprocal Ia inhibition of flexor carpi radialis (FCR) and soleus (SOL) motoneurons was measured (as the depression of the background FCR and SOL EMG activity and as the short latency inhibition of the FCR and SOL H-reflex evoked by radial and peroneal nerve stimulation). In addition, the latency of motor evoked potentials (MEPs) in the FCR muscle and the tibialis anterior (TA) muscle was measured. In the patients, the mean reciprocal inhibition was normal in the arms, while it was significantly decreased in the leg compared with the healthy subjects. In the patients, the average latency of MEPs in the FCR muscle was normal, while the latency to the MEP in TA muscle was significantly longer than that found in healthy subjects. Four patients, however, differed from the other patients by having significant reciprocal inhibition in the leg and a significantly shorter latency of TA MEPs than found in the other patients. The six patients without reciprocal inhibition in the leg instead had significant short latency facilitation of the SOL H-reflex and a longer TA MEP latency than seen in the healthy subjects and in the four patients with retained reciprocal inhibition. These findings support the hypothesis that disynaptic reciprocal inhibition and short latency facilitation are involved in the development of spasticity and, furthermore, they suggest a positive correlation between impairment of corticospinal transmission and decrease of reciprocal inhibition/appearance of reciprocal facilitation.

Keywords: corticospinal tract; reciprocal inhibition; paraplegia; spasticity

Abbreviations: ADPSP = autosomal dominant pure spastic paraparesis; FCR = flexor carpi radialis; MEP = motor evoked potential; MT = motor response threshold; SOL = soleus; TA = tibialis anterior; TMS = transcranial magnetic stimulation.

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Introduction

Impairment of reciprocal inhibition between motoneurons supplying antagonist muscles has long been suspected of contributing to the development of spasticity, and a decreased excitability in the disynaptic reciprocal inhibitory pathway at rest has indeed been demonstrated in several different groups of spastic patients (Yanagisawa *et al*., 1976; Crone *et al*., 1994, 2001, 2003; Okuma *et al*., 2002). In addition, it has been shown that the disynaptic reciprocal inhibition is replaced by a short latency facilitation in some spastic patients with multiple sclerosis, hemiparesis and paraplegia (Okuma *et al*., 2002; Crone *et al*., 2003).

The interneurons interposed in the disynaptic reciprocal inhibitory pathway are activated by the corticospinal tract in both monkey (Jankowska *et al*., 1976) and man (Iles and Pisini, 1992; Nielsen *et al*., 1993) and are strongly facilitated by supraspinal commands before and at the onset of agonist contraction (Crone *et al*., 1987). This movement-related supraspinal facilitation is impaired in patients with spasticity (Morita *et al*., 2001), and decreased supraspinal control of interneurons in the disynaptic reciprocal inhibitory pathway has thus been suggested as one of probably several contributing factors to the development of spasticity.

The hereditary spastic paraplegias (HSPs) are neurodegenerative disorders of the motor system characterized by slowly progressive lower limb spasticity. HSP can be inherited in an autosomal dominant (autosomal dominant pure spastic paraparesis; ADPSP), autosomal recessive or X-linked manner. The neuropathological feature of ADPSP is axonal degeneration that is maximal in the terminal portions of the longest descending and ascending tracts (crossed and uncrossed corticospinal tracts to the legs, fasciculus gracilis fibres and, to a lesser extent, spinocerebellar fibres), while the neuronal cell bodies of the degenerating fibres are preserved. Dorsal root ganglia, posterior roots and peripheral nerves are normal (Behan and Maia, 1974; Bruyn, 1992).

ADPSP is clinically characterized by slowly progressive spasticity and weakness in the legs, hyper-reflexia and Babinski's sign, with little or no involvement of the upper extremities. Comparison of the spinal and supraspinal control of muscle activity in the legs and the arms in these patients may therefore provide valuable information about the pathophysiology of spasticity.

The aim of the present study was to evaluate the excitability in the disynaptic reciprocal inhibitory pathway and the corticospinal transmission in arms as well as legs in ADPSP patients who showed signs of spasticity in the legs but not the arms.

Degeneration of corticospinal axons may be seen as an increase in the latency of leg muscle motor evoked potentials (MEPs) following transcranial magnetic stimulation (TMS). The MEP latency was therefore used to evaluate the corticospinal transmission. Reciprocal inhibition was measured as the depression of the background soleus (SOL) or flexor carpi radialis (FCR) EMG activity and as the short latency inhibition of the SOL or FCR H-reflex. The inhibition was evoked by peroneal nerve and radial nerve stimulation, respectively.

Patients and methods

Patients

The experiments were performed in 10 patients with ADPSP from five different Danish families (six men and four women; average age on first test: 40 ± 14 years). The average height of the patients was 174 ± 7 cm. Families A and B were part of a previous study on clinical, paraclinical and genetic features in ADPSP (Nielsen *et al*., 1998).

None of the patients received any kind of medication. The clinical and genetic data of the patients are summarized in Tables 1 and 2. The patients were tested twice with 4 years between the tests. In the first test, reciprocal inhibition and tibialis anterior (TA) MEP latency were only measured in the leg, whereas measurements were made in the leg as well as the arm in the second test. Control experiments were performed in 15 healthy subjects (10 men, five women; average age: 32 ± 12 years). The average height of the healthy subjects was 178 ± 9 cm.

All patients and healthy subjects gave informed written consent to the experiments, which were approved by the local ethics committee of Copenhagen. All experiments were conducted according to the Declaration of Helsinki.

Molecular genetics

For complete sequencing of the spastin gene, the 17 coding exons and intron–exon boundaries were amplified by polymerase chain reaction (PCR) with the use of primers as described (Hazan *et al*., 1999). PCR products were sequenced with the AmpliTaq® FS Big Dye Terminator Cycle Sequence Kit (Applied Biosystems, Forster City, CA) using the primers and conditions as described by Hazan *et al*. (1999), and analysed on an ABI PRISM 3730 DNA Sequencer (Applied Biosystems).

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 footplate, which was connected to a torque meter. The

Table 1 *Disease characteristics of the 10 subjects included in the study*

Patient no.	Family	*SPG4* mutation	Age at onset (years)	Disease duration (years)
(008)	A	+	17	22
(011)	P	–	1	40
(012)	P	–	1	65
(017)	K	–	3	30
(013)	P	–	1	33
(014)	H	+	50	20
(016)	K	–	40	17
(020)	H	+	30	4
(021)	B	–	18	36
(022)	A	+	32	1

Table 2 *Clinical data of the 10 ADPSP patients*

Patient no.	Patellar reflex left/right	Achilles reflex left/right	Ankle clonus left/right	Muscle tone knee left/right	Muscle tone ankle left/right	Power dorsiflexion left/right	Power plantarflexion left/right
(008)	3/3	2/2	EB/EB	2/2	1/1	5/5	5/5
(011)	3/3	3/3	EB/EB	3/3	3/3	4/4	4/4
(012)	3/3	1(op.)/3	EB/EB	3/4	(op.)/3	4/4	4/4
(017)	3/3	3/3	EB/EB	3/3	3/3	4/4	4/4
(013)	3/3	3/3	EB/EB	3/3	3/3	4/4	4/4
(014)	3/3	3/3	EB/EB	3/3	3/3	5/5	5/5
(016)	3/3	3/3	EB/EB	3/3	3/3	5/5	5/5
(020)	3/3	3/3	EB/EB	3/3	3/3	5/5	5/5
(021)	3/3	3/3	EB/EB	3/3	3/3	4/4	5/5
(022)	3/2	3/3	EB/EB	2/2	3/3	5/5	5/5

The numbers in the table signify values from the left/right leg. It was possible to demonstrate reciprocal inhibition of the soleus H-reflex in the first four subjects in the table. Tendon reflexes were graded as: 0 = absent; 1 = hypoactive; 2 = normal: 3 = hyperactive. EB indicates that there were extra beats when examining for ankle clonus, but that the clonus was not sustained. 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 muscle tone, passive movement difficult; 5 = affected part(s) is rigid in flexion or extension. 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. Op. in the third line indicates that this patient had received orthopaedic surgery to the Achilles tendon.

examined arm was placed in a cushioned groove with the shoulder in neutral position, the elbow in 90° flexion and the wrist in 5° flexion and in mid-position between supination and pronation. The subjects grasped a handle, which was connected to a torque meter. All contractions were isometric. Surface electrodes were used for recording EMG (electromyographic) activity. Three different electrophysiological parameters were measured: (i) the latency of MEPs in the TA and FCR muscles elicited by TMS; (ii) reciprocal inhibition of the SOL and FCR H-reflexes evoked by stimulation of the peroneal and radial nerves, respectively; and (iii) reciprocal inhibition in the voluntary SOL and FCR EMG evoked by stimulation of the peroneal and radial nerves, respectively.

Transcranial magnetic stimulation

TMS was applied by a flat figure-of-eight coil (diameter of the individual loops: 9 cm) placed over either the leg or hand area of the motor cortex, and MEPs in the TA or FCR muscles were recorded. The magnetic stimulator was a Magstim 200 (The Magstim Co., UK). The optimal position for eliciting MEPs in the respective muscles was found at the beginning of the experiment. In general, the best position for evoking the TA MEP was found just lateral to the midline close to Cz, whereas the best position for evoking the FCR MEP was found 4 cm lateral to Cz. In both cases, the handle of the coil pointed backwards. All measurements were performed during a voluntary contraction of the muscle corresponding to 10% of the maximal voluntary strength (determined as the maximal voluntary wrist flexion or ankle dorsiflexion torque that the subject could maintain for 2 s). Five MEPs were averaged for each of 4–5 stimulation intensities between 1.0 and 1.3 times the MEP threshold. The MEP threshold was determined as the intensity at which an MEP larger than 100 μV was seen in 50% of the trials. The MEP latency was measured as the onset of the first deflection above the background activity in the rectified EMG for the average of five MEPs at 1.2 times the MEP threshold.

H-reflex

The FCR H-reflex was evoked by stimulation of the median nerve at the elbow through a bipolar electrode (1 ms rectangular pulse) placed on the medial aspect of the upper arm just above the elbow joint. The two legs of the electrode had plates which were 0.5 × 1 cm in size and separated by 2 cm. The cathode was placed proximally to the cathode. The SOL H-reflex was evoked by stimulating the tibial nerve through a monopolar stimulating electrode (1 ms rectangular pulse). The FCR and SOL 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^2 recording area; 2 cm distance between the poles) placed over the SOL and the FCR muscle. The size of the control SOL H-reflex was in all situations adjusted to 20–25% of M_{max} (the maximal M-response in the SOL muscle; Crone *et al*., 1990). It was not possible to evoke a similarly large FCR H-reflex and this response was therefore adjusted to ~5% of M_{max} in all subjects. It was possible to evoke an FCR H-reflex in only seven of the healthy subjects and four of the patients. Control and conditioned reflexes (see below) were randomly alternated at an interval of 4 s. The data were stored on a computer for later statistical analysis.

Conditioning of the FCR and SOL H-reflex by stimulation of the radial and peroneal nerve

The FCR H-reflex was conditioned by stimulation of the radial nerve through a pair of ball electrodes (2 cm diameter; rectangular 1 ms pulse) placed 5 cm apart on the lateral aspect

of the upper arm. The anode was placed ~10 cm above the elbow joint. The cathode was placed proximally to the anode and the strength of the conditioning stimulation was kept at around 1.0 times the motor response threshold (MT). A time course of the effect of the radial nerve stimulation on the FCR H-reflex was obtained in four patients and seven healthy subjects at rest. The threshold was determined by monitoring the EMG recorded from the extensor carpi radialis muscle and observing movement of the hand.

The SOL H-reflex was conditioned by stimulation of the peroneal nerve (rectangular 1 ms pulse) by bipolar surface electrodes placed 1–3 cm distal to the neck of the fibula. Special care was taken to ensure that the conditioning stimulus was applied at a position where the threshold for the direct motor response in the TA muscle was lower than the threshold for the direct motor response in the peroneal muscles. The specificity of this stimulation was checked repeatedly during the experiments by monitoring the EMG from the TA muscle and palpating the TA tendon. The conditioning stimulus strength was expressed in multiples of the MT in the TA muscle and was kept at 1.0 times the MT. In all subjects, a time course of the effect of peroneal nerve stimulation (stimulation strength 1.0 times the MT) on the SOL H-reflex was investigated at rest (Fig. 1).

Depression of the rectified FCR and SOL EMG by stimulation of the peroneal nerve

In order to measure the amount of depression of the FCR and SOL EMG by stimulation of the radial and peroneal nerves, respectively, the subjects were asked to perform a voluntary wrist flexion or ankle plantarflexion corresponding to 10% of the maximal voluntary wrist flexion or ankle plantarflexion effort (Capaday *et al*., 1990; Petersen *et al*., 1998, 1999). All contractions were isometric. The maximal voluntary wrist flexion and ankle plantarflexion effort were measured as the largest torque that the subject could generate and hold for 2 s (best of three trials with 1 min in between). Reciprocal inhibition of the ongoing FCR and SOL EMGs was measured by averaging the rectified EMGs using the stimulations of the radial and peroneal nerves as trigger. A window from 50 ms prior to the stimulation until 150 ms after the stimulation was averaged. For each stimulus intensity, 75 recordings were averaged. The smallest amount of EMG measured in a window from 30 until 60 ms after the stimulation in the case of the peroneal nerve stimulation and from 20 to 40 ms in the case of the radial nerve stimulation was expressed as a percentage of the background EMG at similar intervals in control trials without stimulation (Fig. 1). Trials with and without stimulation were alternated with each other at a rate of 1 Hz.

Data analysis

The mean and SEM were calculated for all measurements on-line. Differences in the size of the conditioned and control reflexes were tested using Student's *t* test. Differences in the time course of reciprocal inhibition and in the change of inhibition with increased stimulus intensity in ADPSP patients and healthy subjects were tested by a two-way analysis of variance (ANOVA) test. Differences in the latency of MEPs were tested by a one-way ANOVA.

Results

Molecular genetics

The disease was linked to chromosome 2p in all families; however, no mutations were detected in the *SPG4* gene in three families. In family A, a frameshift mutation in exon 5 (832insGdelAA) was found (Nielsen *et al*., 2004) and in family H we found a new mutation in intron 5, predicted to cause abberant splicing of exon 5 which was confirmed by reverse transcription (RT)–PCR analysis of mRNA.

The clinical data of the patients for the leg are summarized in Table 2. No clinical abnormalities were found in the arm of any of the patients except one. This patient had hyperactive biceps, triceps and radialis tendon reflexes bilaterally, but normal muscle tone and force in the arms.

Reciprocal inhibition of the FCR and SOL H-reflex in healthy subjects and ADPSP patients

In the seven healthy subjects in whom an FCR H-reflex could be evoked, the short latency inhibition of the FCR H-reflex evoked by stimulation of the radial nerve (intensity of 1.0 times the MT) had an average size of 44%, i.e. the reflex was depressed to 56% of the control H-reflex size (Fig. 2A; closed circles). In the four ADPSP patients in whom an FCR H-reflex could be evoked, an inhibition of 36% was observed (open circles; there was no statistically significant difference in the inhibition between healthy subjects and patients).

In the healthy subjects, the short latency depression of the SOL H-reflex evoked by stimulation of the peroneal nerve (intensity of 1.05 times the MT) had an average size of ~16% at a conditioning–test interval of 2 ms, i.e. the reflex was depressed to 84% of the control H-reflex size (Fig. 2B, closed circles). It is seen that no reciprocal inhibition of the SOL H-reflex was evoked in the patients (Fig. 2B, open circles). Two-way ANOVA revealed a significantly different inhibition in the patients compared with the healthy subjects ($P < 0.01$).

However, the pooled data from the 10 subjects, who were tested twice with a 4 year interval, concealed that a significant short latency inhibition was in fact observed in four of the patients investigated the first time. Pooled data from all patients are given in Fig. 3A, whereas data from these four patients are given in Fig. 3B. The four patients in whom a significant short latency inhibition was observed did not differ from the other patients in age (mean age: 38.7 versus 39.8 years; $P > 0.1$), they did not belong to one specific family (the four patients belonged to three different families out of the five families participating in the study) and they did not show a larger degree of spasticity (evaluated by the modified

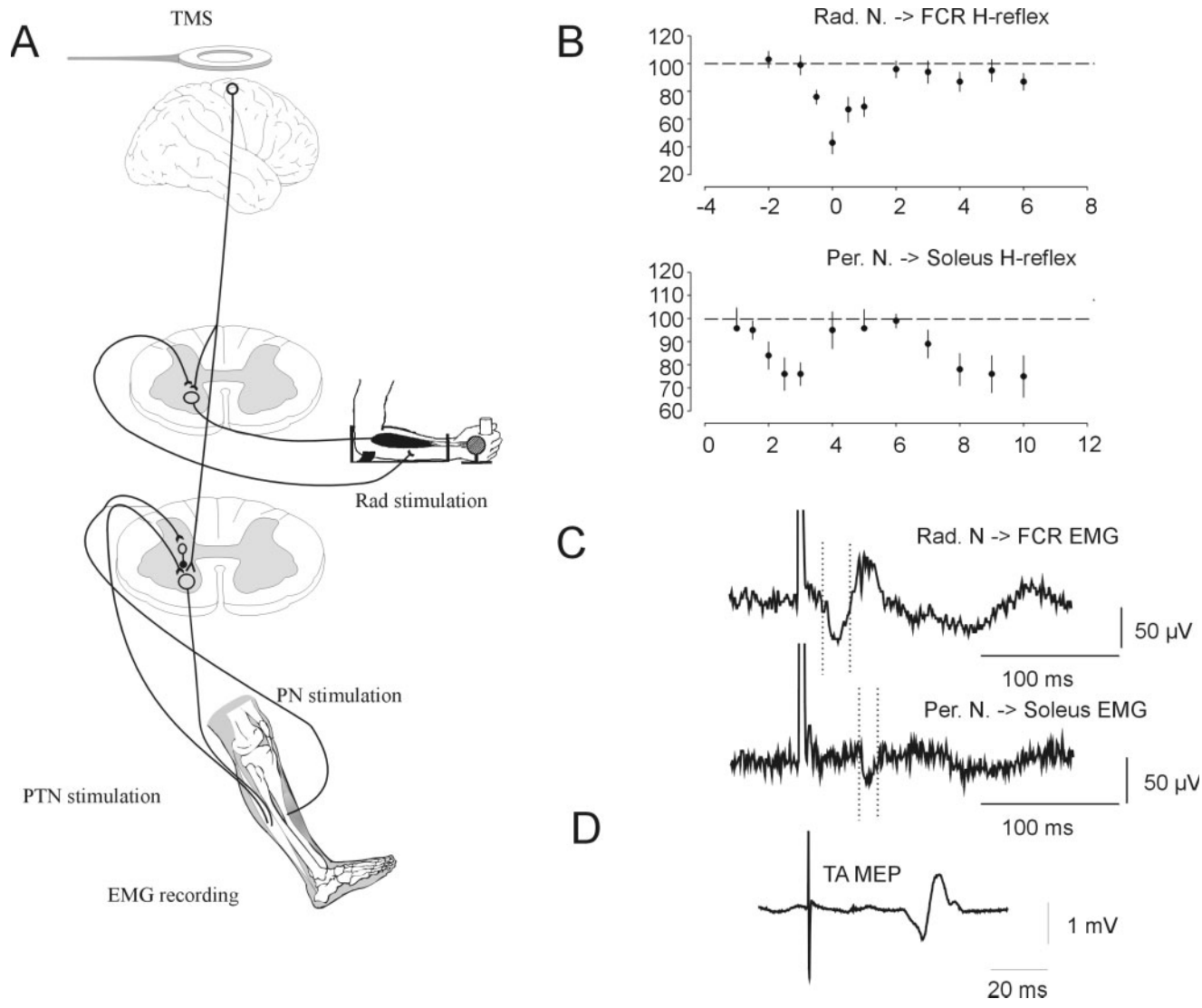

Fig. 1 (**A**) Methodological set-up. Recordings were made from the FCR and SOL muscles. Stimulations were applied to the median, radial, posterior tibial and peroneal nerves. TMS was applied by a figure-of-eight coil placed over the hand or leg area of the motor cortex. MEPs were evoked in the FCR and TA muscles. The upper graph in (**B**) shows a typical time course of the inhibition of the FCR H-reflex evoked by stimulation of the radial nerve in a healthy subject. The lower graph shows a time course of the effect of peroneal nerve stimulation on the SOL H-reflex in a healthy subject. The disynaptic Ia reciprocal inhibition is seen at conditioning–test intervals of ~1–3 ms. In both graphs, the size of the conditioned reflex (with conditioning stimulation) is expressed as a percentage of the control H-reflex size (i.e. without conditioning stimulation). (**C**) The depression of the voluntary rectified FCR EMG (upper graph) and SOL EMG (lower graph) evoked by stimulation of the radial nerve and peroneal nerve, respectively. The vertical dashed lines mark the EMG inhibition. Zero in the graphs is indicated by the horizontal time base, and the vertical bar to the right in graphs indicates the *y* scale. In (**D**), an example of an MEP recorded from the TA muscle is shown.

Ashworth scale). The significant reciprocal inhibition which was seen in the first test in the four patients had disappeared at the second test performed 4 years later (Fig. 2B, open circles). The degree of spasticity in the four patients was not significantly different from that of the other patients at this time either.

Figure 3C shows that the six remaining subjects had no significant inhibition, and that the inhibition was replaced by a statistically significant facilitation of the SOL H-reflex ($P < 0.05$). The facilitation was seen at a conditioning–test interval of 2–5 ms with a maximum at 4 ms.

Depression of the FCR/SOL EMG evoked by stimulation of the radial/peroneal nerve

As seen from Fig. 4A, a similar difference between reciprocal inhibition around the ankle and wrist joint was found when reciprocal inhibition was evaluated by the voluntary SOL and FCR EMG activity. In both cases, the subjects were asked to make a plantarflexion or wrist flexion corresponding to 10% of the maximal voluntary effort for the two muscles. In the 15 tested healthy subjects, the inhibition in the SOL EMG was seen already at stimulus intensities of 0.9 times the MT and reached a maximal size at stimulation intensities of 1.2 times

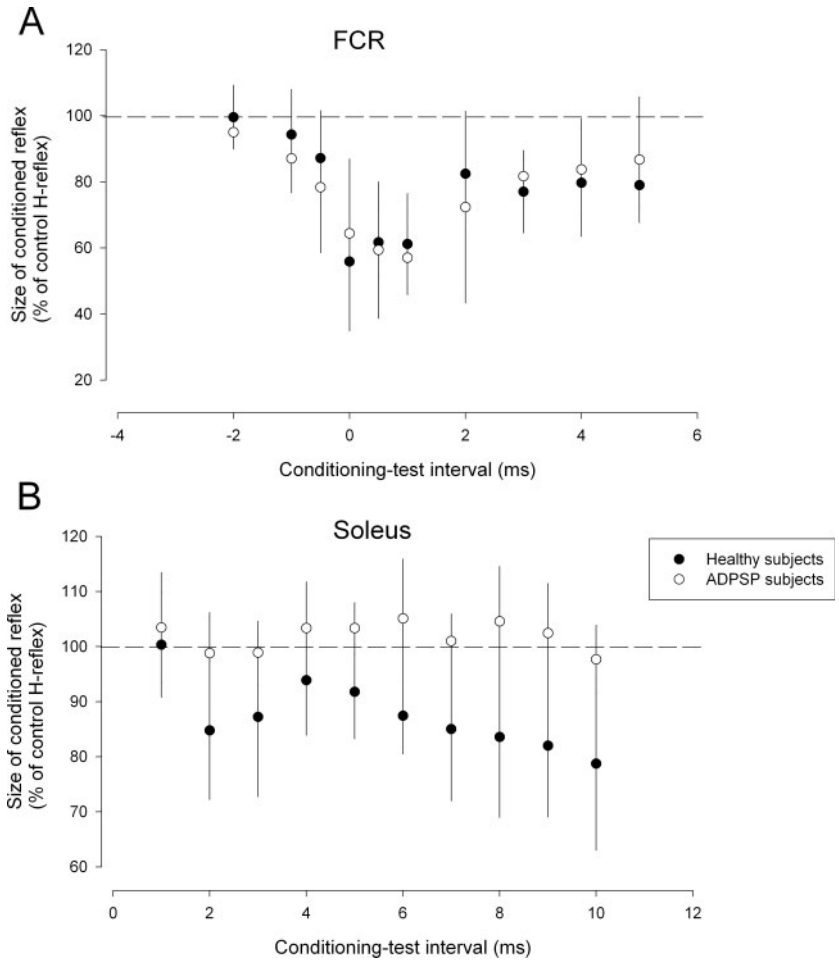

Fig. 2 Reciprocal inhibition of the FCR (**A**) and SOL H-reflex (**B**) in healthy subjects (●) and ADPSP patients (○). In the arm, the test stimulus was an electrical stimulus to the median nerve and the conditioning stimulus was a weak electrical stimulus to the radial nerve. In the leg, the test stimulus was an electrical stimulus to the tibial nerve, and the conditioning stimulus an electrical stimulus to the peroneal nerve (1.05 times the MT). The abscissa indicates the time interval in milliseconds between the conditioning stimulus and the test stimulus, and the ordinate the size of the conditioned SOL H-reflex as a percentage of the unconditioned reflex. **A** shows data from the arm, **B** shows data from the leg.

the MT (EMG measured during inhibition was 55% of the background EMG activity at this intensity). In the 10 ADPSP patients, the inhibition just reached a statistically significant level at 1.2 times the MT, but even at 1.3 times the MT an inhibition of <10% of the background EMG activity was observed. In contrast, the inhibition of the FCR EMG activity produced by radial nerve stimulation had a threshold at ~0.9 times the MT for both the 15 healthy subjects and the 10 ADPSP patients. At higher stimulation intensities, the inhibition increased more in the healthy subjects than in the ADPSP patients and at 1.2 times the MT the FCR EMG activity was inhibited to 48% of the background FCR EMG activity, while the EMG activity was inhibited to 69% in the ADPSP patients. This difference was just statistically significant ($P < 0.05$). Inspection of the individual data from the patients revealed that the main reason for this difference was two subjects in whom no inhibition was observed, whereas significant inhibition of a similar size to that in healthy subjects was observed in the remaining eight subjects. One of these two subjects differed from the other patients by having increased tendon reflexes not only in the legs but also in the arms.

In Fig. 5, the latency and threshold of the MEPs in the FCR and the TA muscles are shown. The mean TA MEP latency measured in the first test in the 10 ADPSP patients was 37.4 ± 4.6 ms, which was significantly longer than in healthy subjects where the average latency was 32.2 ± 2 ms; $P < 0.001$. The mean threshold of the TA MEP in the patients was 61 ± 6.6% of maximal stimulator output in the first test, which was higher than the threshold in the healthy subjects (mean: 44 ± 13.1% of stimulator output; $P < 0.01$). In the second test, the mean TA MEP latency was 38.4 ± 4.4 ms and the threshold 62 ± 9.2%. None of the measures were significantly different from the result in the first test ($P = 0.99$), but still different from the observations in healthy subjects ($P < 0.01$). The mean MEP latency in the four patients who had a significant disynaptic reciprocal inhibition in the first test was calculated. In the first test,

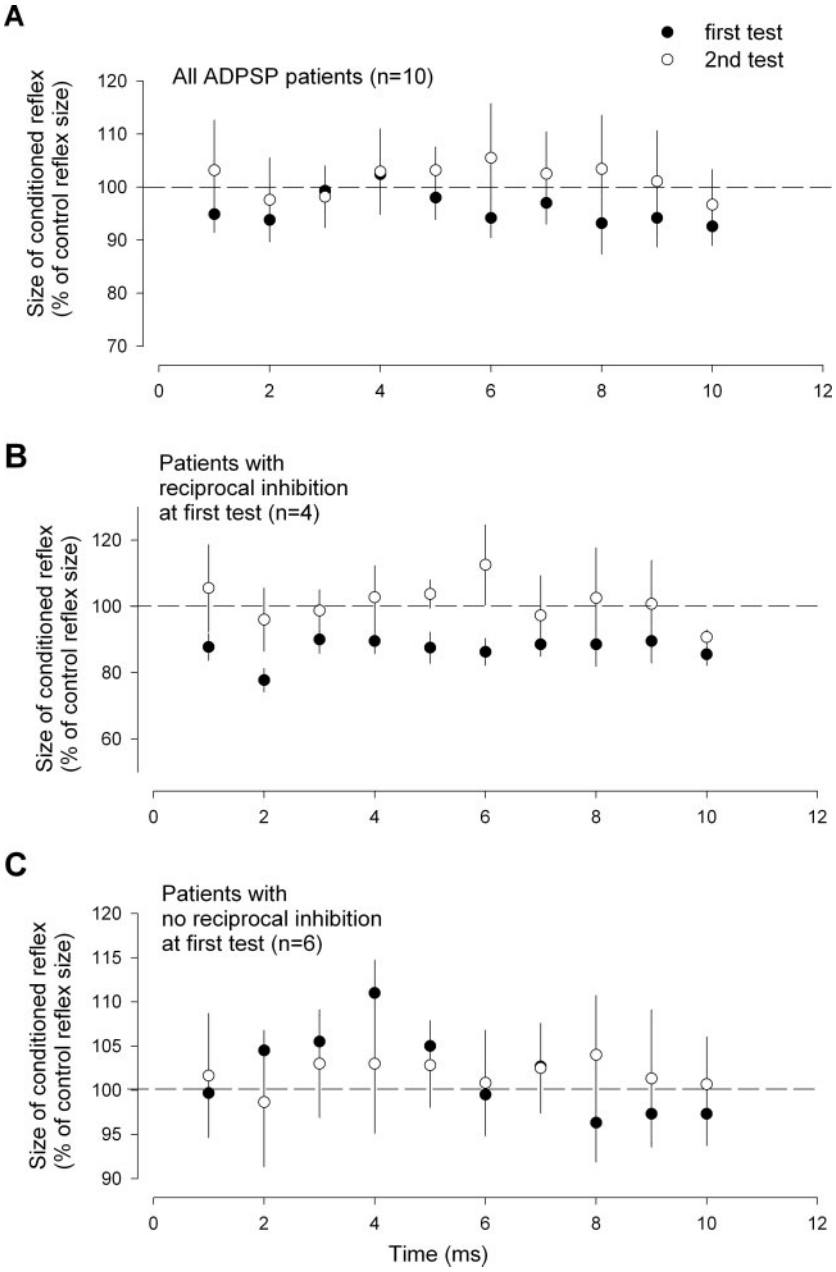

Fig. 3 Reciprocal inhibition of the SOL H-reflex in healthy subjects and ADPSP patients. The inhibition was evoked by a weak (1.05 times the MT) electrical conditioning stimulus applied to the peroneal nerve at the knee. The abscissa gives the time interval in milliseconds between the conditioning stimulus and the test stimulus (to the tibial nerve), and the ordinate the size of the conditioned SOL H-reflex as a percentage of the unconditioned reflex. **A** shows data from all patients, **B** shows data from the four patients in whom reciprocal inhibition was observed at the first test, and **C** shows data from the remaining six subjects.

the mean latency of the TA MEP in these four patients was significantly shorter than the mean latency calculated in the other six patients (average latency: 34.0 versus 40.3 ms; $P < 0.05$). In the second test, this difference had disappeared. The threshold of the MEP of the four patients was not different from that of the other subjects in any of the tests.

For the FCR MEP, no difference was found between the patients and the healthy subjects with regards to either latency or threshold (Fig. 5A and C). However, it should be pointed out that the one subject who showed hyperactive tendon reflexes in the arm is the patient with a much longer FCR MEP latency (36 ms) seen in Fig. 5. As already mentioned, this patient was also different from the other patients by having no reciprocal inhibition in the arm.

The amplitude of the MEPs in both TA and FCR varied between 3 and 25% of M_{max}. No significant differences were found between patients and healthy subjects.

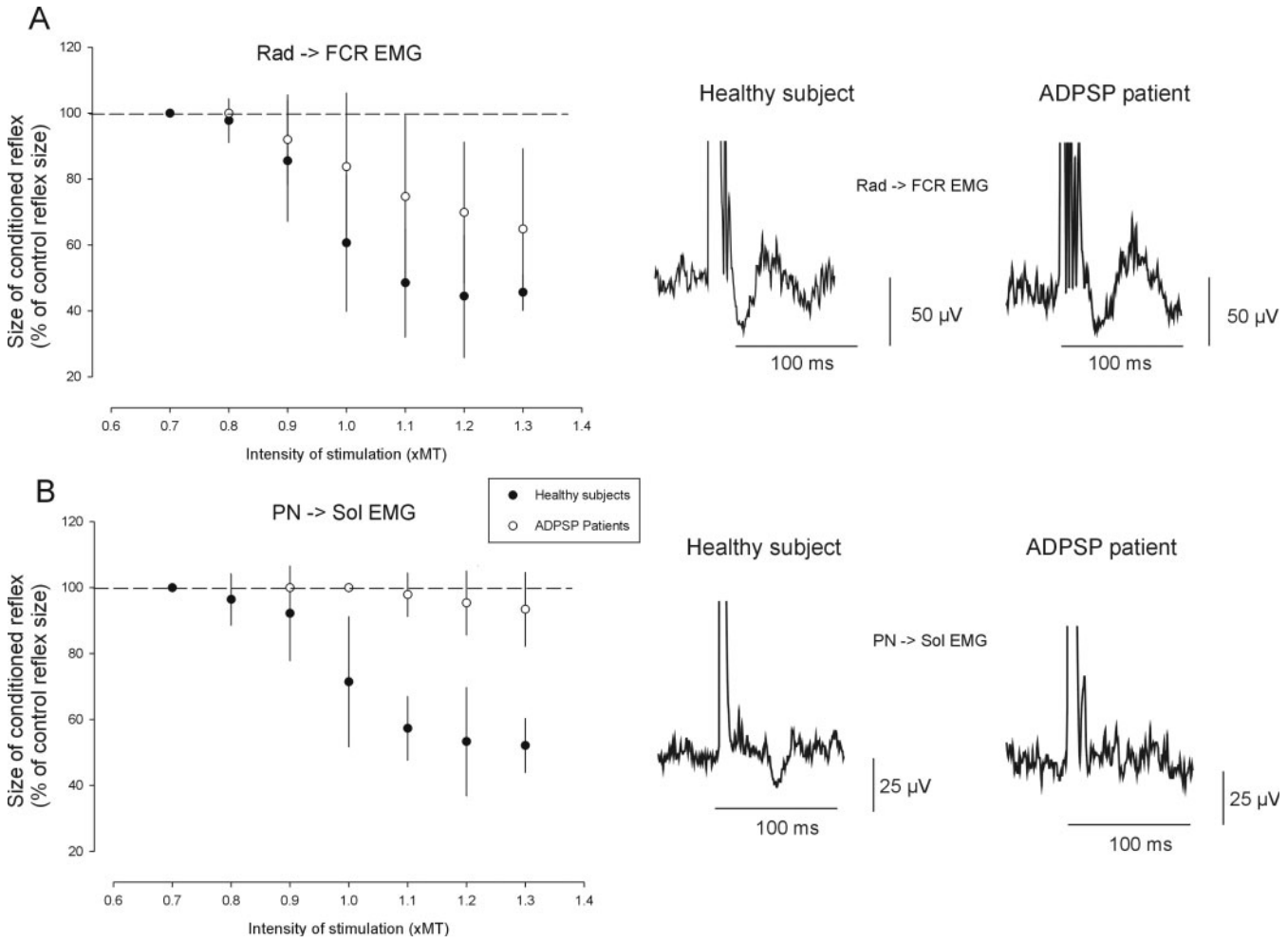

Fig. 4 The amount of depression of the voluntary FCR (**A**) and TA EMG (**B**) following stimulation of the radial nerve and peroneal nerve, respectively. Open circles are pooled data from the ADPSP patients, whereas the closed circles are pooled data from the healthy subjects. The vertical bars are the standard error of the population mean. The amount of inhibition is given as the size of the EMG measured as a percentage of the background (baseline) EMG activity. The subjects were in all cases asked to maintain a contraction corresponding to 10% of the maximal voluntary wrist flexion or dorsiflexion effort. The abscissa is the intensity of the conditioning stimulations. Sample data for a healthy subject and an ADPSP patient are shown to the right of the graphs.

Discussion

In the present study of ADPSP patients with spasticity in the legs and no symptoms in the arms, the main findings are (i) that the patients have significantly less mean disynaptic reciprocal inhibition between ankle flexor and extensor muscles than is found in healthy subjects, but a normal degree of reciprocal inhibition in the arms except for two patients; and (ii) that the patients have significantly longer mean TA MEP latencies than healthy subjects, but normal FCR MEP latencies. Furthermore, in four patients, it was found that at a time when they still had significant reciprocal inhibition in the legs they also had significantly shorter TA MEP latencies than the patients without reciprocal inhibition. Moreover, one patient who had hyperactive reflexes in the arms had significantly longer FCR MEP latencies than the rest of the patients who had no symptoms in the arms.

The spastic paraplegia linked to chromosome 2p in all families; however, we did not detect mutations in three of the families, which may be accounted for by mutations in non-coding regions such as the promotor region or polyadenylation site, and not all families with linkage to the *SPG4* locus do have mutations in the *SPG4* gene (Lindsey *et al*. 2000).

Independent of the mutation status, we did not find a correlation between age at onset, duration of the disease, Ashworth scale, progressive/non-progressive form and the electrophysiology.

Disynaptic reciprocal inhibition

The present observations on disynaptic reciprocal inhibition consolidate findings from many previous studies, which have shown that reciprocal inhibition is impaired in patients with spasticity of different origin (Yanagisawa *et al*., 1976; Artieda *et al*., 1991). Several studies have shown decreased reciprocal inhibition in spastic limbs in patients suffering from multiple sclerosis (Crone *et al*., 1994; Morita *et al*., 2001),

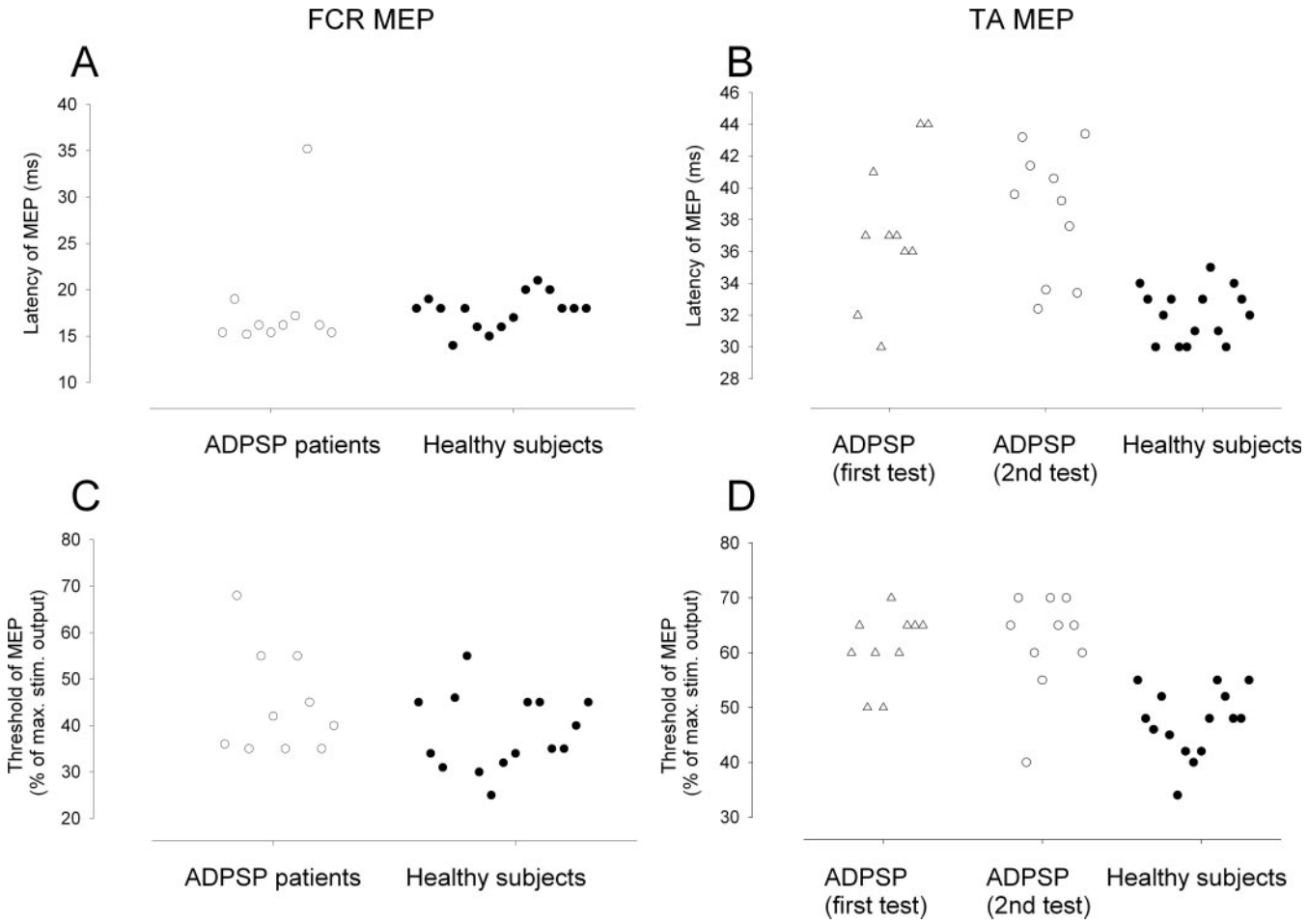

Fig. 5 The latency (**A** and **B**) and threshold (**C** and **D**) of MEPs evoked by TMS in healthy subjects (closed circles) and ADPSP patients (open symbols). Each symbol represents one subject. Measurement of the latency and threshold of the TA MEPs was performed at the first (▵) as well as the second test (○) in the ADPSP patients.

in hemiparetic patients due to vascular disease (Artieda *et al*., 1991; Panizza *et al*., 1995; Crone *et al*., 2003) and in patients with spinal cord injury and spastic paraparesis (Okuma *et al*., 2002). The observation in the ADPSP patients that the clear signs of spasticity in the legs are accompanied by a lack of reciprocal inhibition while no abnormalities with regards to reciprocal inhibition are found in the arms with normal clinical findings adds further support to the hypothesis that the disynaptic reciprocal inhibitory pathway plays a role in the development of spasticity.

The hypothesis seemingly may be contradicted by the observation that the four patients with retained short latency reciprocal inhibition in the legs (when tested the first time) were not more spastic than the patients with impaired reciprocal inhibition and by the fact that their spasticity had not increased 4 years later when the reciprocal inhibition had disappeared. However, since many patients were so spastic that the grading (according to the modified Ashworth scale) had already reached maximum at the first test, the lack of difference may be explained by an early 'saturation' problem of the evaluation method rather than a true lack of difference.

Another finding in the present study is that the disynaptic reciprocal inhibition between ankle flexors and extensors, when lacking, is replaced by facilitation with a slightly longer duration than the disynaptic inhibition. The facilitation described in the ADPSP patients has also been described previously in patients who developed spasticity after a cerebral vascular insult, in patients who developed paraplegia and spasticity after a spinal cord injury (Okuma *et al*., 2002; Crone *et al*., 2003) and in patients with multiple sclerosis (Crone *et al*., 1994). The facilitation has never been found in normal subjects. The neuronal pathway mediating this facilitation has not yet been established, but it has been suggested that it is mediated by the Ib facilitatory pathway (Crone *et al*., 2003). It should be noted that in the four patients with retained inhibition, the inhibitory phase was never followed by a facilitatory phase and that this was also the case in the second test where it was not possible to demonstrate any reciprocal inhibition. The findings in the present study thus support the hypothesis that the short latency facilitation is involved in, but not a prerequisite for, the development of spasticity.

It thus seems reasonable to suggest that impairment of disynaptic reciprocal inhibition/appearance of facilitation is one of perhaps several pathophysiological mechanisms involved in the development of spasticity. However, the supraspinal mechanisms of the alteration in the excitability of this pathway have not yet been elucidated, but the findings in the present study clearly suggest a positive correlation between impairment of cortical transmission and decreased disynaptic reciprocal inhibition. This is also in keeping with the observation that the supraspinal control of the disynaptic reciprocal (spinal) pathway has been found to be impaired in spastic patients suffering from multiple sclerosis (Morita *et al*., 2001).

Altogether these results corroborate the hypothesis that the disynaptic reciprocal inhibitory pathway plays a role in the pathophysiology of spasticity, and the results suggest a close relationship between the corticospinal transmission being affected and decrease of reciprocal inhibition.

Further studies of inhibitory pathways during natural voluntary movements (e.g. walking) must be performed in spastic patients in order to elucidate the functional importance of the impaired inhibition.

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