

Facilitation of transmission in heteronymous group II pathways in spastic hemiplegic patients

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Abstract

Objective—A potent heteronymous group II excitation of quadriceps motor neurons has been recently demonstrated in normal subjects. The present study was undertaken to investigate whether this heteronymous group II excitation also contributes to spasticity in hemiplegic patients.

Method—The early and late facilitations of the quadriceps H reflex elicited by a conditioning volley to the common peroneal nerve at three times motor threshold, attributed to non-monosynaptic group I and group II excitations respectively, were investigated. The comparison was drawn between results obtained in 20 patients after stroke, with hemiplegia due to a vascular lesion in the territory of the middle cerebral artery, and 20 age and sex matched normal subjects.

Results—A significant increase in the group I as well as in the group II common peroneal nerve induced facilitation of the quadriceps H reflex was seen on the spastic side of the patients (group I: 159 (SEM 10)% of control H reflex; group II: 165 (SEM 8)%) compared with their unaffected side (group I: 126 (SEM 4)%; group II: 128 (SEM 5)%) (Wilcoxon signed rank test, $p < 0.01$), or to the right (group I: 132 (SEM 4)%; group II: 131 (SEM 5)%) or left (group I: 130 (SEM 3)%; group II: 135 (SEM 6)%) side of controls (Mann-Whitney U test, $p < 0.01$). No significant correlation (Spearman rank test) was found between the degree of group I and group II induced facilitations on the spastic side of the patients and the degree of clinically assessed spasticity (Ashworth scale).

Conclusion—These results reflect a facilitation of the transmission in the interneuronal pathway coactivated by group I and group II afferents, probably resulting from a change in their descending control in spastic hemiplegic patients.

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Muscle spindle primary endings innervated by rapid Ia afferents are activated by both static and dynamic components of muscle stretch, whereas secondary endings activated by slower group II afferents are only sensitive to the static component of muscle stretch.¹ An increased Ia excitation, whether reflecting γ hyperactivity, decrease in presynaptic inhibition of Ia termi-

nals, or homosynaptic depression,^{2–4} has been extensively discussed as a cause of the exaggeration of the stretch reflex which characterises spasticity. By contrast, the possible role of exaggerated group II excitation has generally not been considered. This is probably for two reasons: (1) the ease with which Ia effects may be explored, because they are the first to reach motor neurons and have the lowest electrical threshold, contrasting with the absence of available methods for investigating group II pathways, has certainly led to the overestimation of the role of the first and an underestimation of the second; (2) the classic asymmetry of group II actions with dominating flexor excitation and extensor inhibition found in anaesthetised low spinal cats⁵ seemed not to be compatible with the distribution of spasticity to extensors in the lower limb of patients with hemiplegia.

In fact, the main response evoked by stretch in ankle and foot muscles of normal subjects is a spinal reflex mediated by group II muscle afferents^{6–8} and a contribution from group II pathways to the exaggerated quadriceps stretch reflex of paraplegic patients has been suggested.⁹ A potent heteronymous group II excitation of quadriceps motor neurons has also been demonstrated in normal subjects after stimulation of the common peroneal nerve.^{10–11} The present research was undertaken to investigate whether this heteronymous group II excitation also contributes to spasticity in hemiplegic patients.

Methods

PATIENTS

The experiments were carried out on 20 post-stroke patients with hemiplegia (13 men and seven women, mean age 56 (SD 14 years). Nineteen patients were right handed, one ambidextrous (handedness was determined by questionnaire¹²). A control group consisted of 20 healthy right handed subjects age (53 (SD 11) years, student's $t = 0.8226$ for 38 df) and sex matched (11 men, nine women, $\chi^2 = 0.104$ with Yates' correction, 1 df). The subjects gave informed consent to the experimental protocol, which had been approved by the local ethics committees.

The patients were selected on the basis of the following criteria: a first right or left sided motor deficit of abrupt onset affecting the leg due to a single vascular lesion (19 ischaemias, one haematoma) in the territory of the middle cerebral artery, and existence of spasticity of the quadriceps muscle assessed by Ashworth's scale. The motor deficit was assessed at a screening visit using three validated indexes:

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the trunk control test, motricity index, and Ashworth's modified scale.¹³ The leg tone was assessed by the sum of Ashworth's score of four groups of muscles: knee flexors (hamstrings) and extensors (quadriceps), ankle flexors, and extensors (table). The patients did not receive any antispastic drugs at the moment of the study. Three of them were previously taking antispasticity medication (dantrolene), which was stopped for at least 4 weeks before the screening visit.

EXPERIMENTAL PROCEDURE

General experimental arrangement

The subjects were comfortably seated in an armchair with the hip semiflexed (60°), the knee slightly flexed (10–20°), and the ankle at 20° plantar flexion.

Recording

Electromyographs were obtained by surface electrodes 2 cm apart secured to the skin over the muscle belly of the vastocruureus (15–20 cm above the patella on the anterior aspect of the thigh) and of the tibialis anterior (medial part of the anterior aspect of the leg).

Quadriceps H reflex

The quadriceps H reflex was induced by stimulating (rectangular shocks of 1 ms duration, 0.25 Hz) the femoral nerve percutaneously. The active cathode (half ball 2 cm diameter) was in the femoral triangle and the reference electrode under the buttock. The intensity of the test stimulus was first progressively increased to obtain a stable maximum H reflex on the oscilloscope screen while the size of the unconditioned H reflex was stable at about 20% of its maximal amplitude. In each experimental run, corresponding to a given interstimulus interval (ISI), 20 unconditioned (control) and conditioned reflexes were randomly alternated. Reflex responses were measured peak to peak¹⁴ and analysed by computer on line, the result being stored on disk for further analysis. Conditioned reflexes were expressed as a percentage of control reflexes.

Clinical features and clinical assessment of the 20 poststroke hemiplegic patients

Patient	Sex	Age (y)	Duration (months)	Side of hemiplegia	Motricity index	Trunk control test	Q tonus	Leg tonus
1	M	58	2	Right	45	61	3	16
2	M	50	2	Left	51	48	3	17
3	F	25	4	Left	74	100	3	20
4	M	60	1	Left	145	100	1	10
5	M	66	2	Left	121	100	2	10
6	F	44	4	Left	86	61	2	15
7	F	47	5	Left	133	87	2	10
8	M	76	4	Left	113	61	3	17
9	M	46	1	Right	135	100	1	5
10	F	37	13	Left	81	74	3	20
11	M	47	24	Right	151	100	1	5
12	F	67	6	Right	114	100	1	6
13	M	65	11	Left	86	61	3	17
14	M	66	3	Right	151	100	1	8
15	M	57	3	Right	80	48	1	12
16	F	37	2	Right	56	48	4	22
17	M	70	3	Left	141	65	3	15
18	F	70	5	Left	71	48	4	18
19	M	77	2	Left	60	61	4	21
20	M	59	4	Left	33	48	1	14

Motricity index: score max 200; trunk control test: score max 100; Q tonus=degree of spasticity of the quadriceps muscle assessed by Ashworth's scale; Leg tonus=addition of Asworth's scale of four groups of muscles: quadriceps, hamstrings, ankle flexors and extensors.

For each patient interstimulus intervals (ISIs) used were randomly alternated from nine to 25 ms. In the same way, the order of the side tested (spastic or non-spastic) was randomly determined for each patient.

The Hmax/Mmax ratio and the ratio between threshold intensities of H and M responses were measured comparatively on both sides in six patients.

Conditioning stimulus

Electrical pulses of 1 ms duration were delivered to the common peroneal nerve through bipolar surface electrodes (1 cm diameter silver plate electrodes 2 cm apart). The common peroneal nerve was stimulated at the level of the caput fibulae at a site where the threshold for the M response was lower for the tibialis anterior than for the peroneal muscles, in which there was, however, a response when the stimulation was increased at three times motor threshold. The current was measured by a current probe (Textronix 602) and expressed in multiples of the intensity for motor threshold. It was verified by tendon palpation that stimulation of the common peroneal nerve at three times motor threshold did not produce any contraction of muscles other than those innervated by the common peroneal nerve—that is, did not encroach on another nerve.

Cutaneous stimuli

The cutaneous sensation (weak local or radiating paraesthesia) evoked by stimulation was mimicked by pure cutaneous stimuli to estimate the contribution of cutaneous afferents. The local sensation was reproduced by plate electrodes placed 3 cm more laterally than the nerve trajectory or on the dorsal aspect of the foot over the nerve projection area (allowance was made for the extra peripheral conduction time). The stimulus intensity was adjusted to imitate the strong but not painful sensation evoked by common peroneal nerve stimulation at three times motor threshold.

STATISTICS

To determine in each subject whether the changes evoked in the H reflex amplitude by the conditioning stimulation were significant, analysis of variance (ANOVA) using Scheffe's method was performed. The Wilcoxon signed rank test was used for the comparison between the values of H reflex amplitude of the spastic and non-spastic side of the patients or between the left and right side of the control subjects. The Mann-Whitney *U* test was used to compare the values obtained in the two populations (patients and control subjects). The correlation between the amount of the common peroneal nerve induced facilitation of quadriceps H reflex and the ranking according to Ashworth's scale or the motricity scale was evaluated using the Spearman rank test.

Results

COMMON PERONEAL NERVE INDUCED

FACILITATION OF THE QUADRICEPS H REFLEX

In fig 1, the comparison is drawn between the time course of the changes in the quadriceps H

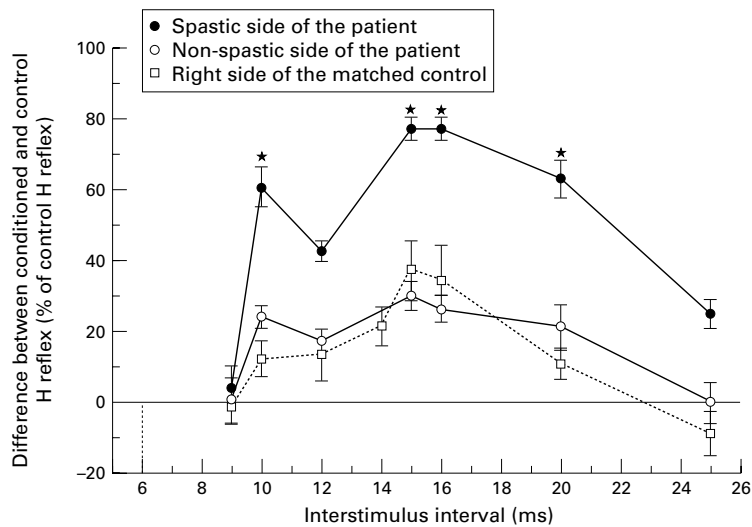


Figure 1 Time course of facilitation of the quadriceps H reflex elicited by stimulation of the common peroneal nerve at three times motor threshold. The difference between the size of common peroneal nerve conditioned and control quadriceps H reflexes (expressed as a % of the control H reflex) is plotted against the conditioning test interval. Data are from a hemiplegic spastic patient and his age matched control. The vertical dotted line indicates the ISI corresponding to the simultaneous arrival at the segmental spinal level of the conditioning and test Ia volleys. Each symbol represents the mean of 20 measurements. Vertical bars=1 SEM; * $p < 0.05$. The comparison is made between results obtained on the spastic side, the non-spastic side, and on the right side of the age matched control. In the three cases, the size of the control H reflex was about 20% of the maximum M response.

reflex amplitude elicited by a stimulation of the common peroneal nerve at three times motor threshold in a control subject, and on the unaffected and spastic side of a patient with hemiplegia. As described in normal subjects,¹⁰ there was a biphasic facilitation of the quadriceps H reflex with an early facilitation at 10–12 ms ISI and a late peak at 15–20 ms ISI, which are attributed to group I and group II afferents, respectively (see discussion). When allowance was made for the difference in afferent conduction times of conditioning (elicited more distally) and test Ia volleys they were expected to arrive simultaneously at the spinal level at 6 ms ISI, which corresponds therefore to 0 ms central delay. The early facilitation of the quadriceps H reflex peaking at 10 ms ISI (4 ms central delay) was much larger ($p < 0.05$, Scheffe's method) on the spastic side of the patient (160 (SEM 5)% of the control value) than on the non-spastic side (124 (SEM 2)% of the control value) or in the control subject (112 (SEM 5)% of the control value). The late facilitation peaking 5 ms later (15 ms ISI) was also much larger ($p < 0.05$, Scheffe's method) on the spastic side of the patient (178 (SEM 4)% of the control value) than on his non-spastic side (131 (SEM 4)% of the control value) or in the control subject (137 (SEM 8)% of the control value). At 25 ms ISI the late facilitation was over in the control subject or on the non-spastic side of the patient, whereas it was still present, albeit decreased, on the spastic side.

Figure 2 shows a sample of 20 conditioned (continuous line) and 20 control (dotted line) H reflexes obtained in one hemiplegic patient and one control subject at two ISIs (10 ms A-B-C, 16 ms D-E-F). The conditioned H reflex was larger on the spastic side (A, D) than on the non-spastic side (B, E) or on the right

side of the control (C, F) in both delays. This was better displayed on the right side of fig 2 where the differences between the mean amplitude of the 20 conditioned and 20 control reflexes were compared between spastic side (bold line), non-spastic side (thin line), and right side of the control (dotted line) at each ISI (G-H).

Common peroneal nerve induced effects were assessed at ISI 9, 10, 12, 15, 16, 18 and 20 ms on both sides of the 20 hemiplegic patients and of the 20 control subjects.

A significant ($p < 0.05$, Scheffe's method) group I induced facilitation was found in 80% and 90% of the control subjects on the right (16/20) and left side (18/20), respectively, in 90% of the patients on the spastic side (18/20), and in 80% of them on the unaffected side (16/20). The group II induced facilitation was found to be significant ($p < 0.05$, Scheffe's method) in 90% and 80% of the normal subjects (right side: 18/20 and left side: 16/20) and 95% and 75% of the patients (spastic side 19/20 and unaffected side: 15/20). The group I induced peak was significantly ($p < 0.05$, Scheffe's method) larger on the spastic than on the unaffected side in 12 out of 18 patients and the group II induced peak in 15 out of 19 patients.

Mean results (SEM) are given in fig 3. The mean differences between conditioned and control H reflexes (expressed in % of control H reflex) are plotted against the different ISIs tested. The mean of the maximum difference of group I and group II induced facilitations within the windows 9–12 ms and 15–20 ms are shown in respectively the fourth and ninth bar chart groups. The mean group I induced facilitation (at ISIs 10 and 12 ms) was significantly larger in the spastic than in the unaffected side ($p < 0.05$, Wilcoxon signed rank test) of patients and than in right or left sides of normal subjects ($p < 0.05$, Mann-Whitney U test). The mean group II induced facilitation (at ISIs 15, 16, 18 and 20 ms) was significantly larger in the spastic than in the unaffected side ($p < 0.01$, Wilcoxon signed rank test) of patients and than in right or left sides of normal subjects ($p < 0.01$, Mann-Whitney U test). By contrast, no significant differences were found, either for group I or group II induced facilitations, between the right or left side of the controls (Wilcoxon signed rank test) or between the unaffected side of the patients and controls (Mann-Whitney U test).

ABSENCE OF CUTANEOUS INDUCED EFFECTS

As in normal subjects,¹⁰ it was ascertained on the spastic side of six hemiplegic patients that a pure cutaneous stimulation of the skin above the caput fibulae or on the dorsal aspect of the foot mimicking the sensation elicited by common peroneal nerve stimulation at three times motor threshold did not evoke any significant quadriceps H reflex changes.

MODERATE ASYMMETRY IN THE EXCITABILITY OF THE MONOSYNAPTIC H REFLEX ARC

Contrasting with the very marked asymmetry of the common peroneal induced facilitation of the quadriceps H reflex between affected and

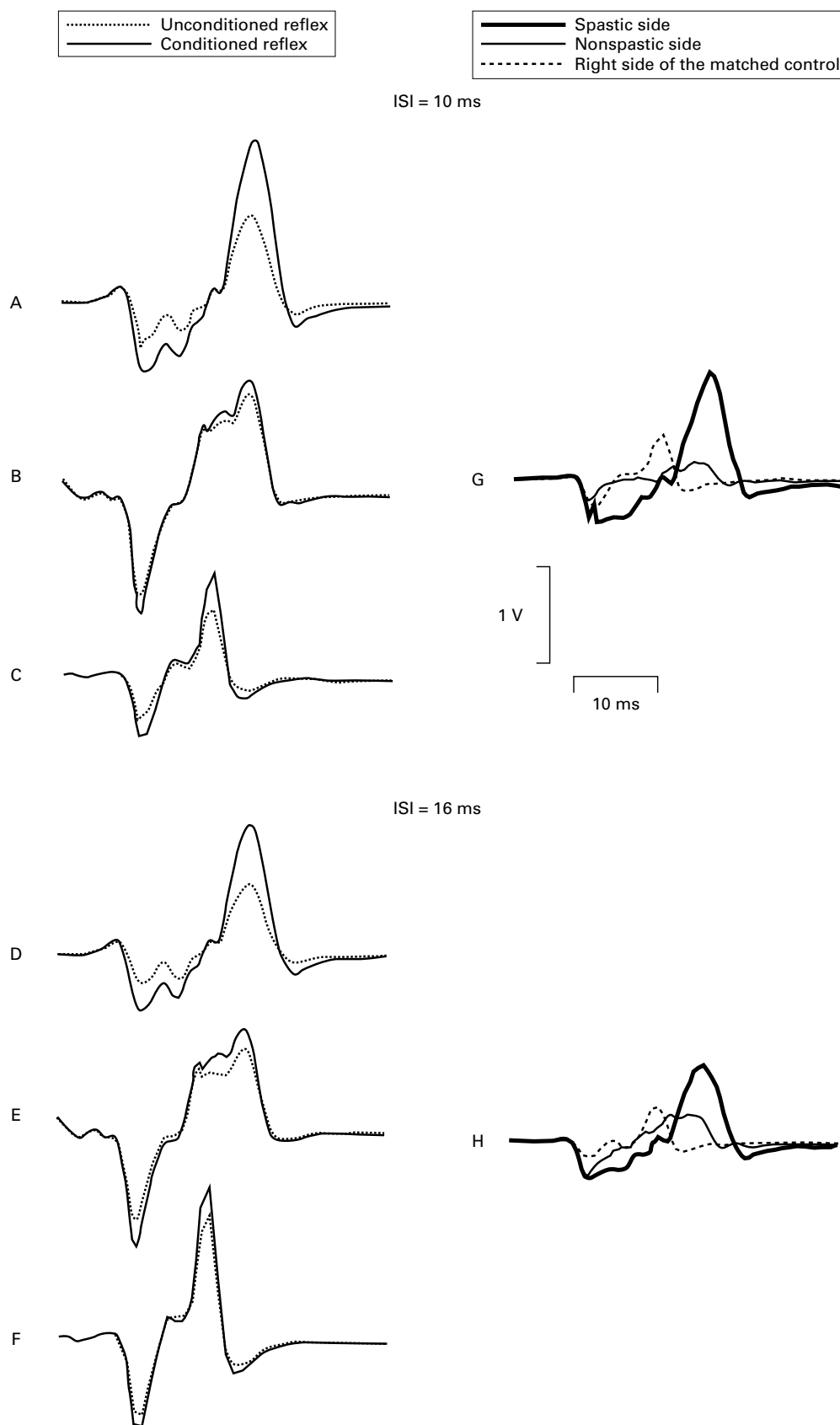


Figure 2 Raw data from a hemiplegic and a control subject. Left: Average EMG recording within the window 10–50 ms after femoral nerve stimulation, obtained on the spastic side (A, D) and on the non-spastic side (B, E) and on the right side of a control (C, F), at two different ISIs (10 and 16 ms). Dotted line=control H reflex (without common peroneal nerve stimulation); continuous line=conditioned H reflex. Each trace represents the average of 20 EMG responses. H reflex was preceded by M response. Size of control H reflex about 20–30% of the size of H max (3 V spastic side; 4 V non-spastic side; 4 V control subject). Right: differences between conditioned and control reflexes on the spastic side (bold line), the non-spastic side (thin line), and the control subject (dotted line), at the same ISIs (10 ms G, 16 ms H).

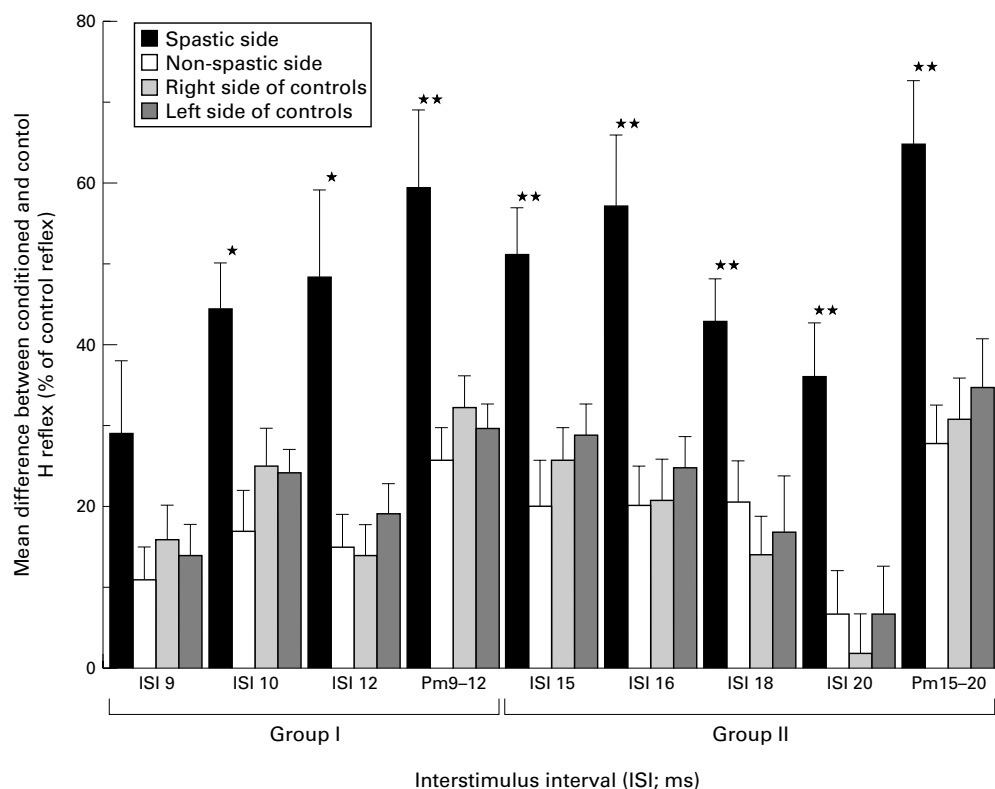


Figure 3 Mean values (SEM) of quadriceps H reflex group I and group II facilitations. Mean values are expressed as a % of the control H reflex. Vertical bars = SEM. ISI = interstimulus interval (ms) between the common peroneal and femoral nerve stimulations; bars Pm9-12 and Pm15-20 = mean of the peak max of group I and group II facilitations respectively. Statistically significant differences between spastic, non-spastic sides and controls * $p < 0.05$; ** $p < 0.01$.

unaffected sides, the asymmetry concerning the excitability of the monosynaptic reflex arc was only moderate in the six patients in whom it was assessed: mean ratio H max/M max equal to 66 and 55%, respectively; mean ratio between threshold intensities of H and M responses equal to 0.95 and 1.06, respectively.

ABSENCE OF CORRELATION BETWEEN THE AMOUNT OF COMMON PERONEAL INDUCED FACILITATION AND CLINICAL FEATURES

No significant correlation (Spearman's rank test) was found between the degree of group I and group II induced facilitations on the spastic side of the patients and the degree of clinically assessed spasticity (Ashworth scale) or the motor impairment (trunk control test and motricity index).

Discussion

ORIGIN OF THE EARLY AND LATE FACILITATIONS OF THE QUADRICEPS H REFLEX AFTER COMMON PERONEAL NERVE STIMULATION

In normal subjects stimulation of the common peroneal nerve evokes two peaks of facilitation both in the quadriceps H reflex and in the poststimulus time histogram of single voluntarily activated quadriceps motor units.¹⁰ The early low threshold ($0.6 \times \text{MT}$) peak is attributable to non-monosynaptic group I excitation¹⁵ mediated through an oligosynaptic pathway, the long central delay (3-4 ms) of the effect being explained by the rostral location of the relevant premotor neurons with respect to motor neurons.¹⁶ The characteristics of the

second peak (higher threshold, late latency increasing more than that of the early peak when the common peroneal nerve is cooled) are consistent with a group II effect.^{10, 11}

Convergence of group II and group I afferents has been shown in the feline lumbar enlargement onto common intermediate zone/ventral horn interneurons mediating disynaptic excitation to motor neurons,¹⁷⁻¹⁹ and indirect arguments suggest that group I and group II excitations might also be mediated through common interneurons in humans. This might explain the highly significant negative correlation found between group I and group II induced facilitations of the quadriceps H reflex at rest: a large recruitment of common interneurons by the common peroneal group I volley would make them unresponsive to the following group II volley (occlusion)¹⁶; similarly, the finding that the onset of the group II induced excitation of quadriceps motor neurons is delayed when the interneurons activated by group I fibres are inhibited on the combined actions of cortical and group I volleys,²⁰ is consistent with a mediation of excitatory effects of group I and group II afferents via common interneurons.

POSSIBLE MECHANISMS UNDERLYING THE INCREASED COMMON PERONEAL INDUCED FACILITATION OF THE QUADRICEPS H REFLEX IN PATIENTS WITH HEMIPLEGIA

The increase in the common peroneal induced facilitation of the quadriceps H reflex found on the affected side of patients with hemiplegia

may have three possible origins: (1) increased excitability of α motor neurons; (2) decreased common peroneal induced presynaptic inhibition of Ia terminals mediating the afferent volley of the quadriceps test reflex; (3) facilitation of the transmission in the pathway coactivated by common peroneal group I and II afferents.

Hyperexcitability of α motor neurons

If the increased excitability of α motor neurons (final common motor pathway) was the only mechanism responsible for the increased common peroneal induced facilitation, the response of quadriceps motor neurons would be expected to be exaggerated to the same extent whatever the input. The finding that the difference between affected and unaffected side was much larger for common peroneal induced facilitation than for response to the Ia input from quadriceps (as estimated by H max/M max and H threshold/M threshold ratios) suggests that the α motor neuronal hyperexcitability is not the only mechanism responsible for the increased common peroneal induced facilitation.

Decreased common peroneal induced presynaptic inhibition of Ia terminals

The common peroneal afferent volley elicits a presynaptic inhibition of Ia terminals mediating the afferent volley of the quadriceps H reflex²¹⁻²³ and the common peroneal induced quadriceps H reflex facilitation is the net result of this presynaptic inhibition and of the postsynaptic excitatory effects seen above.¹⁰ A decrease in presynaptic inhibition in spastic patients could therefore be partly responsible for the increased common peroneal induced facilitation of the H reflex. In fact, in the leg of hemiplegic patients, neither common peroneal induced presynaptic inhibition of Ia terminals to soleus motor neurons²⁴ nor presynaptic inhibition of heteronymous Ia afferents from quadriceps to soleus²⁵ are decreased, and the decrease in vibratory inhibition in these patients²⁶ is due to a reduction of the postactivation depression.^{4 24}

Facilitation of transmission in the pathway activated by common peroneal afferents

A facilitation of the transmission in the pathway coactivated by common peroneal group I and group II afferents seems thus likely. This may result from a change in one (or several) of the controls exerted on this pathway: (1) γ activity; (2) specific descending monoaminergic control of group II afferents^{27 28}; (3) presynaptic inhibition of afferents synapsing with premotor neurons²⁹; (4) descending controls of the relevant premotor neurons.³⁰

Hyperexcitability of static γ motor neurons—could produce a greater tonic discharge of muscle spindle afferents from pretibial flexors (statically stretched because of the 20° plantar flexion) than in normal subjects and thus an increase in the excitability of the relevant premotor neurons. However, available data concerning the responses of Ia afferents to static stretches showed no differences between

normal and spastic patients and thus no evidence for a change in activity of static γ motor neurons in spastic patients.^{31 32}

A disruption of the monoaminergic inhibitory descending control—which is specific of group II afferents by a presynaptic mechanism^{27 28} seems unlikely as the early peak, purely group I in origin, was similarly enhanced. However, because of the static stretch due to the ankle position there was a tonic discharge from group II afferents, and the resulting volley, if its efficiency in activating premotor neurons is increased by a reduction of the normal monoaminergic inhibitory descending control, might tonically increase the excitability of the premotor neurons and also contribute to enhance their response to the group I volley.

A decrease in presynaptic inhibition of group I and group II afferents synapsing with premotor neurons—must also be considered. Given the absence of changes in presynaptic inhibition of Ia terminals projecting monosynaptically on motor neurons mentioned above in the spastic lower limb, this seems unlikely. However, it has been shown at the cervical level that the descending control is different during voluntary movement on Ia afferents projecting on motor neurons and on premotor neurons.³³

An increase in the excitability of the relevant lumbar premotor neurons—resulting from a change in their descending control, might well account for the finding that the early and late peaks were similarly increased. In this respect, it must be pointed out that it has been shown in normal subjects that corticospinal stimulation elicits a twofold effect on these premotor neurons with excitation and inhibition.²⁰ A disruption of the balance between these opposite effects because of the lesion might explain the increased common peroneal induced facilitation.

CLINICAL CORRELATIONS

The absence of any statistical correlation between the clinical scores of spasticity assessed by the Ashworth's scale and the amount of increase in common peroneal-induced facilitation of the H reflex may be explained by two possibilities:

(1) The experimental paradigm used in the electrophysiological investigation explored heteronymous group II projections from the tibialis anterior on to quadriceps motor neurons, whereas spasticity was clinically assessed in homonymous pathways activated by quadriceps stretch. It is possible that the transmission in homonymous and heteronymous pathways is not increased to the same extent.

(2) Ashworth's scale measures hypertonia by gauging the resistance to passive displacement of the limb but this method cannot distinguish between the peripheral contribution due to changes in mechanical properties of the muscle resulting from motor impairment³⁴⁻³⁶ and the neural contribution due to hyperexcitability of group II pathways.

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