Impaired efficacy of spinal presynaptic mechanisms in spastic stroke patients

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Pathophysiological mechanisms underlying spasticity have been the subject of many studies. These studies performed in various kinds of spastic patients have revealed abnormalities in many spinal pathways controlling motoneurone discharge. Unfortunately, the pathophysiological mechanisms responsible for the development of spasticity remains nevertheless largely unknown since most of the previous studies failed to reveal a link between the characteristics of spasticity (severity, time course) and that of the dysfunction of a given perturbed spinal pathway. In the present series of experiments, we focused on the study of presynaptic mechanisms acting at the synapse fibre Ia—motoneurone since monosynaptic reflexes are enhanced in spasticity. Two presynaptic mechanisms have been described in both animals and humans: presynaptic Ia inhibition and post-activation depression. By increasing the number of subjects in comparison with previous studies (87 patients and 42 healthy controls) we have been able to show that these two mechanisms are unequally impaired in stroke patients depending on (i) the duration of the disease (acute, defined as less than 3 months after the causal lesion, or chronic, defined as more than 9 months after the causal lesion), (ii) the side considered (affected or unaffected) and (iii) the severity of spasticity. In this respect, only post-activation depression amount was found to be highly correlated with the severity of spasticity. Although not a definitive proof, this correlation between severity of spasticity and changes in a given spinal pathway lead us to conclude that the impairment of post-activation depression is likely one of the mechanisms underlying spasticity. On the contrary, changes in presynaptic Ia inhibition appear to be a simple epiphenomenon, i.e. a basic correlate of the brain lesions. It is argued that plastic changes develop from the disuse due to motor command impairment in both pathways.

Keywords: spasticity; presynaptic Ia inhibition; post-activation depression; upper and lower limbs; stroke

Abbreviations: ACA = anterior cerebral artery; PAD = primary afferent depolarization; PCA = posterior cerebral artery; FCR = Flexor Carpi Radialis; Sol = Soleus; CPN = Common Peroneal Nerve; HC = Healthy Controls

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Introduction

Patients with brain lesions often display hypertonia, or spasticity, a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex (Lance, 1980). Efficacy of transmission in many spinal pathways has been extensively investigated in spastic patients in resting state (for reference, see Pierrot-Deseilligny, 1990; Dietz, 1992; Pierrot-Deseilligny and Burke, 2005; Nielsen et al., 2007), including postsynaptic pathways [Ib inhibition (Delwaide and Oliver, 1988), recurrent inhibition (Katz and Pierrot-Deseilligny, 1982; Mazzocchio and Rossi, 1997), disynaptic reciprocal Ia inhibition (Crone et al., 1994, 2003, 2007)] and presynaptic mechanisms [presynaptic Ia inhibition (Nakashima et al., 1989; Faist et al., 1994; Aymard et al., 2000; Kagamihara and Masakado, 2005), post-activation depression (Nielsen et al., 1995; Aymard et al., 2000; Schindler-Ivens and Shields, 2000; Masakado et al., 2005; Grey et al., 2008)].

Although the transmission throughout some of these pathways have been found to be modified to a variable extent depending on the kind of diseases and on the level of
the CNS lesion, contradictory results have been reported in the literature for the same pathway. Furthermore, although dysfunction of these inhibitory mechanisms might be partially responsible for spasticity, most of these studies failed to report a positive correlation between the magnitude of these dysfunctions and the severity of spasticity.

In this study, we focused on the regulation of presynaptic mechanisms since a decrease of their activity would increase the efficacy of the stretch-induced Ia volley in firing motoneurones and might therefore be responsible for stretch reflex exaggeration.

It was postulated (Delwaide, 1973) that H reflex depression produced by a prolonged vibration of homonymous tendon reflected the excitability of PAD interneurones mediating presynaptic inhibition of Ia terminals. Because this reflex depression is decreased in most spastic patients, it became generally accepted that there was a decrease in presynaptic inhibition of Ia terminals with PAD in these patients (Delwaide, 1973; Ashby et al., 1980; Calancie et al., 1993; Childers et al., 1999). However, conditioning vibration applied to the homonymous tendon activates another presynaptic mechanism, post-activation depression, which also contributes to the vibratory-induced depression of the reflex (Katz et al., 1977; Crone and Nielsen, 1989; Hultborn et al., 1996). Indeed, it has long been known that stimulus rate has a long-lasting depressive effect on the size of the test reflex (Magladery and Mc Dougall, 1950). This depression occurs without concomitant changes in membrane potential or conductance (Hultborn et al., 1996); this phenomenon can be attributed to the repetitive activation of the Ia—motoneurone synapse because it is also observed after a conditioning stimulus that is subthreshold for the H reflex or tendon jerk (Taborikova and Sax, 1969; Crone and Nielsen, 1989; Hultborn et al., 1996) and is likely to involve changes in readily releasable transmitter operating within presynaptic terminals (Lev-Tov and Pinco, 1992; Li and Burke, 2001). Therefore, this homonymous vibration-induced depression cannot be used to estimate selectively presynaptic inhibition of Ia terminals with PAD (Hultborn et al., 1987). The problem is accentuated by the fact that post-activation depression, induced by passive stretch of the test muscle or by varying the stimulus rate, has been found significantly decreased in spastic patients with spinal cord injury (Calancie et al., 1993; Nielsen and Hultborn, 1993; Aymard et al., 2000; Schindler-Ivens and Schields, 2000; Masakado et al., 2005; Grey et al., 2008), multiple sclerosis (Nielsen et al., 1995; Grey et al., 2008) and on the affected side of patients with hemiplegia (Aymard et al., 2000, Masakado et al., 2005). However, the development of reliable methods allowing the selective assessment of presynaptic inhibition of Ia terminals [electrically induced D1 inhibition (Mizuno et al., 1971; El-Tohamy and Segwick, 1983; Berardelli et al., 1987) and heteronymous monosynaptic Ia facilitation (Hultborn et al., 1987)] permitted to explore the relative contributions of post-activation depression and presynaptic Ia inhibition to the malfunction of the monosynaptic reflex arc. Thus, in the upper limb, radial-induced inhibition of the FCR was found to be (i) decreased on the affected side (Nakashima et al., 1989; Artieda et al., 1991; Aymard et al., 2000) and, to a lesser extent, on the unaffected side (Aymard et al., 2000) of patients with hemiparesis after stroke and (ii) completely disappeared in two patients with tetraplegia due to spinal cord lesion at C5–C6 (Aymard et al., 2000). In contrast, in the lower limb, presynaptic Ia inhibition was found to be (i) without significant differences between the affected and unaffected sides of hemiplegic patients after stroke, and of the same magnitude as in healthy controls (HC) (Aymard et al., 2000) or contradictorily reduced on the affected side with respect to HC (Kagamihara and Masakado, 2005) and (ii) consistently depressed in patients with spinal cord lesions due to multiple sclerosis (Nielsen et al., 1995), amyotrophic lateral sclerosis (Pierrot-Deseilligny, 1990) and traumatic injuries (Faist et al., 1994). However, the number of patients included in these previous reports was rather small and, as highlighted by Pierrot-Deseilligny and Burke (2005), this might be responsible for conflicting results and for making a positive correlation between the impaired efficacy of a given spinal mechanism and the exaggeration of the stretch reflex unlikely. Therefore, the first aim of this study was to explore the efficacy of presynaptic spinal mechanisms on Sol and FCR motor nuclei in a greater population of hemiplegic patients and HC in order to disclose a possible correlation between the extent of the decreased efficacy in presynaptic mechanisms and the intensity of spasticity.

Spasticity is not an immediate consequence of CNS lesions, nor is it typically present in the acute stages of diseases. Rather, spasticity begins to emerge typically several weeks after the causal lesion (whether a spinal or a brain lesion).

The question then arises whether, and to what extent, presynaptic spinal mechanisms become impaired over time in stroke patients. The second aim of this investigation was to examine the differences that occur in post-activation depression and presynaptic Ia inhibition in both cervical and lumbar levels among HC, acute stroke patients (<3 months after the causal lesion) and chronic stroke patients (>9 months after the causal lesion).

Methods

Subjects

Experiments were performed on 42 healthy controls (27 female and 15 male) aged 19–59 (mean and SEM 35 ± 10.6 years) and on 87 stroke patients (39 female and 48 male) aged 21–75 (50.8 ± 12.3 years). However, not all the subjects participated in every experiment. All of whom had given their written informed consent to the experimental procedure which had been approved by the institutional local ethics committee and conformed with the guidelines in the Declaration of Helsinki.
Figure 1 describes the population of patients studied. In addition, detailed background information of the patients examined is available as a Supplementary material.

All the patients had suffered a de novo stroke. Cerebral lesions were systematically visualized on computed tomography or MRI of the brain: 69 of the lesions were unilateral focal lesions (32 in right hemisphere, 37 in left hemisphere) and 18 were bilateral, although the former exhibited unilateral clinical symptoms. Sixty-three patients had suffered a cerebral infarction and 24 a cerebral haemorrhage. At the time of the investigation,
the duration of the illness varied from 6 days to 288 months (median = 6.5 months). In all of the experiments but one, only monohemispheric stroke patients were included. Patients exhibiting bilateral lesions were only included in the last set of experiments, i.e., correlation between the impaired efficacy of presynaptic mechanisms and the intensity of spasticity, to increase the power of analysis. To investigate time-related changes of presynaptic mechanisms following stroke, two aged-matched groups of patients were constituted: (i) a group of acute stroke patients (<3 months after CNS lesion) which consisted of 20 patients aged 49±15.8 years with a median duration of the disease of 2 months and (ii) a group of chronic stroke patients (>9 months after CNS lesion) composed of 27 patients aged 49.8±10.6 years with a median duration of the disease of 17 months. In all subjects, the degree of spasticity at ankle or at wrist was estimated from 1 to 5 using Ashworth scale (Ashworth, 1964). Taking into account the heterogeneous distribution of the scores among the population, patients with scores of 4 and 5 were pooled for statistical analysis.

General experimental arrangement

The subjects were comfortably seated in an armchair. The shoulder was in slight abduction (60°), the elbow semi-flexed (110°) and the forearm was pronated and supported by the arm of the chair. The examined leg was loosely fixed with the hip semi-flexed (120°), the knee slightly flexed (160°) and the ankle at 110° plantar flexion.

H reflexes

The Sol and the FCR H reflexes were recorded from pairs of non-polarizable electrodes (0.8 cm² silver plates 1.5 cm apart) secured to the skin over the corresponding muscle bellies. Percutaneous electrical pulses of 1 ms duration at a frequency of 0.33 Hz were delivered through surface electrodes: bipolar electrodes (1.5 cm diameter half-balls 2 cm apart) to the median nerve in the cubital fossa; unipolar electrode to stimulate the posterior tibial nerve (active cathode in the popliteal fossa, anode on the anterior aspect of the knee). The signals were amplified and filtered (Tektronix TM503A, bandwidth 0.1–1 kHz). The reflex responses were measured as peak-to-peak amplitude of the non-rectified reflex and the data were stored on a computer for subsequent statistical analysis.

The sensitivity of the H reflex to conditioning facilitatory and inhibitory effects has been shown to depend crucially on its control size (Crone et al., 1990). Hence, except when a patient was reluctant to endure the unpleasant feeling accompanying the strong stimulation to elicit maximal motor response, M_max and H_max were determined in each case. The unconditioned test reflex was adjusted to be ~H_max/2 in the side first explored (dominant for healthy subjects) and adjusted in the other side to be similar in percentage of M_max. In patients in which M_max could not be recorded, the unconditioned test value was adjusted to ~H_max/2, taking into account the results obtained in the other patients (see Results section; Aymard et al., 2000).

Method of assessing post-activation depression at the Ia afferent—motoneurone synapse

As in previous investigations (Hultborn and Nielsen, 1998; Aymard et al., 2000; Lamy et al., 2005), post-activation depression at the homonymous Ia fibre-motoneurone synapse was studied by exploring the depressive effect of increasing the stimulus rate on the size of H reflexes (Fig. 2A and B). The depression of the H reflex is dramatic at short intervals (1–2 s between two consecutive stimuli) with a rapid recovery up to 8 s, although at least 15 s are required to completely extinguish this depression (Crone and Nielsen, 1989; Lamy et al., 2005).

In this study, the ratio of the H reflex amplitude, evoked at high and low stimulus rates, was calculated in each case. Thus, the amount of post-activation depression of the FCR and the Sol H reflexes was assessed as the size of the H reflex elicited every 2 s (high stimulus rate) and expressed as a percentage of its value when elicited every 8 s (low stimulus rate). This is referred to as the 2/8 s ratio and allowed us to statistically compare the results between stroke patients and HC; the greater the 2/8 s ratio, the smaller the post-activation depression. At least 20 H reflexes (after elimination of the first) at 2 and 8 s were evoked. Special care was taken over recording sessions to assure that the target muscle was at complete rest during testing since post-activation depression is decreased during voluntary contraction of the tested muscle (Hultborn and Nielsen, 1998).

Method of assessing presynaptic Ia inhibition

Presynaptic Ia inhibition mediating the afferent volley of the test reflex (FCR or Sol) is responsible for a late inhibition [the so-called D1 inhibition (Mizuno et al., 1971)] of the H reflex evoked by an electrical volley to group I afferents in the nerve supplying muscles antagonistic to the test motoneurone pool. The resulting reflex depression depends on the excitability of PAD interneurones: the larger this excitability, the greater the presynaptic inhibition of the test afferent volley and the greater the reflex depression. Thus, electrical stimulation of the radial nerve or the common peroneal nerve (CPN) evokes in FCR motoneurones and Sol motoneurones respectively an early and short-lasting inhibition due to disynaptic inhibition, followed by a long-lasting (D1) inhibition attributed to presynaptic inhibition of the Ia terminals mediating the afferent volley of the H reflex since it has been shown not to be paralleled by a depression of the cortically evoked response in FCR (Berardelli et al., 1987) or Sol (Faist et al., 1996) motoneurones (Fig. 3A and B). Conditioning stimuli were percutaneous electrical stimuli applied through bipolar electrodes. In the upper limb, the radial nerve was stimulated in the spiral groove [single shock of 1 ms duration, intensity 0.95 times the motor threshold (kMT), 13 ms interstimulus interval (Berardelli et al., 1987; Aymard et al., 2000)]. CPN was stimulated at the neck of the fibulae with a train of three shocks [300 Hz, 1 ms duration, 1.2KMT, 21 ms interstimulus interval (Mizuno et al., 1971; El-Tohamy and Sedgwick, 1983; Faist et al., 1996)].

Data analysis

For each series of experiments (20 reflexes when the amplitude of monosynaptic reflexes per se was tested; 40 reflexes when conditioned and unconditioned reflexes were alternated), the mean value of unconditioned and conditioned test reflexes was determined with its SEM. For each population and for each presynaptic mechanism, normality was checked using Kolmogorov-Smirnov and equality of variances tests. Comparisons between both sides within the same population were made using paired t-tests. Pairwise comparisons between HC and stroke patients were
made using unpaired t-tests. The mean age of the HC was younger than stroke patients. However, using a Spearman’s correlation coefficient, we failed to demonstrate any significant effect of age in HC on the efficacy of both presynaptic Ia inhibition (radial-induced depression of FCR H reflex: \( r = -0.1, P = 0.57 \); CPN-induced depression of FCR H reflex: \( r = 0.02, P = 0.9 \)) and post-activation depression (FCR: \( r = -0.12, P = 0.58 \); Sol: \( r = -0.25, P = 0.22 \)).

**Fig. 2** Depression of FCR (left panels) and Sol (right panels) H reflexes following a preceding homonymous reflex discharge in healthy controls (C and D) and stroke patients (E and F). (A and B) Wiring diagram of pathways of postactivation depression of FCR (A) and Sol (B) H reflexes and example of waveforms obtained at 2 and 8 s in one representative healthy subject. Y-shape bars represent excitatory synapse. (C–F) Individual values (thin line) and mean (thick line, values indicated beside the vertical line) of 2/8 s ratios obtained (i) on the dominant (left vertical line) and non-dominant (right vertical line) sides from 20 healthy subjects in the FCR (C) and from 26 subjects in the Sol (D), (ii) on the affected (left vertical line) and unaffected (right vertical line) sides from 19 stroke patients in the FCR (E) and from 17 stroke patients in the Sol (F). (G and H) Comparison between the mean values of the 2/8 s ratios of the FCR (G) and Sol (H) on the affected side (dark grey columns), unaffected side (middle grey columns) of stroke patients and the mean values (dominant + non-dominant) of HC (open columns). Each bar is the average of mean data (±1 SEM). Asterisks indicate significant differences. \( n = \) number of subjects; NS = not significant; **\( P < 0.01 \); ***\( P < 0.001 \); ****\( P < 0.0001 \).
ANOVA (analysis of variance) and ANCOVA were employed. The factors tested are explained in more details in Results section. Conditional on a significant \( F \)-value, post hoc \( t \)-tests (Fisher’s PLSD) adjusted for multiple comparisons using the Bonferroni correction were used to explore the strength of main effects. To examine the relationship between the severity of spasticity and the impairment in the efficacy of presynaptic mechanisms, Spearman’s correlation coefficient test was employed.

**Fig. 3** DI inhibition of the FCR (left panels) and Sol (right panels) H reflexes elicited by electrical stimulation of the nerve supplying antagonistic muscles in healthy controls (C and D) and stroke patients (E and F). (A and B) Wiring diagram of pathways of presynaptic inhibition with PAD of Ia FCR (A) and Sol (B) terminals and example of waveforms from one representative healthy subject. Excitatory synapses are represented by Y-shape bars and inhibitory synapses by small filled circles. (C–F) Individual and mean values of the conditioned value of the H reflex (expressed as a percentage of its control value) obtained (i) on the dominant and non-dominant sides from 32 healthy subjects for the FCR H reflex (C) and from 39 subjects for the Sol H reflex (D), (ii) on the affected and unaffected sides from 39 stroke patients for the FCR H reflex (E) and from 29 stroke patients for the Sol H reflex (F). (G and H) Comparison between the mean values of the DI inhibition of the FCR (G) and Sol (H) on the affected (dark grey columns) and unaffected (middle grey columns) sides of stroke patients and the mean values (dominant + non-dominant) in healthy controls. Asterisks indicate significant differences. \( n = \) number of subjects; NS = not significant; \( * P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001. \)
Results
Impaired efficacy of presynaptic mechanisms in monohemispheric stroke patients

$H_{\text{max}}/M_{\text{max}}$ ratio
As stated in Methods section, in a first step, $M_{\text{max}}$ and $H_{\text{max}}$ were determined at 0.33 Hz in order to adjust the unconditioned test value on both sides (dominant and non-dominant for HC, affected and unaffected for patients). In HC, the mean FCR $H_{\text{max}}/M_{\text{max}}$ ratio was 33.86 ± 18.34% ratio on the dominant side and 34.83 ± 19.8% on the non-dominant side. The mean Sol $H_{\text{max}}/M_{\text{max}}$ ratio was 47.68 ± 23.10% on the dominant side and 51.32 ± 22.42% on the non-dominant side. In patients, the mean FCR $H_{\text{max}}/M_{\text{max}}$ ratio was 53.56 ± 23.59% on the affected side and 34.46 ± 22.09% on the unaffected side (23 subjects). The mean Sol $H_{\text{max}}/M_{\text{max}}$ ratio was 54.09 ± 29.68% on the affected side and 41.49 ± 22.42% on the non-affected side (15 subjects). In patients in whom $M_{\text{max}}$ could not be recorded, the unconditioned test reflex was adjusted to $\sim H_{\text{max}}/2$. This was assumed taking into account that the mean value of the unconditioned test reflex ranged from 16.87% (healthy control, dominant side) to 27.04% (patients, affected side) for the Sol H reflexes obtained in both dominant and non-dominant sides: FCR (32 subjects, $P=0.16$) and Sol (39 subjects, $P=0.47$). In stroke patients, mean radial-induced depression of the FCR H reflex (G) was significantly decreased on the affected side with respect to the unaffected side ($P<0.0001$) or HC ($P<0.0001$). Similarly, the mean CPN-induced depression of Sol H reflex (H) was also found to be reduced on the affected side with respect to the unaffected side ($P<0.04$) or to HC ($P<0.0005$). In addition, both the radial- and CPN-induced depressions of the FCR and Sol reflexes on the unaffected side (G and H) were also significantly smaller, although to a lesser extent, than in HC (FCR: $P<0.0006$; Sol: $P<0.04$). Individual results in (E and F) show that asymmetry was observed in most of the patients (35/39 for the FCR and 21/29 for the Sol). Overall, these results suggest that the impairment of presynaptic Ia inhibition behaves similarly in the upper and lower limbs. However, note for discussion that reduced presynaptic Ia inhibition is more marked at cervical (G) than at lumbar (H) segments.

Post-activation depression
In Fig. 2, frequency-related depressions of the FCR (left panels) and Sol (right panels) H reflexes were assessed in HC (C and D) and stroke patients (E and F). In HC (C and D) individual values (thin line) and mean (thick line, values indicated beside the vertical line) of 2/8 s ratios obtained in the dominant and non-dominant sides are shown. Paired t-tests revealed that whatever the motor nucleus, there was no significant asymmetry of 2/8 s ratios between the mean values obtained in the dominant and non-dominant sides: FCR (FCR: 20 subjects, $P=0.71$; Sol: 26 subjects, $P=0.63$). Thus, to allow comparison between HC and patients (G and H), the mean values of (dominant + non-dominant) 2/8 s ratios were calculated for both FCR and Sol motor nuclei. In stroke patients, mean values of the 2/8 s ratios (G and H) were found to be significantly increased (i.e. the post-activation was decreased) on the affected side (dark grey columns) in both the upper and the lower limbs when compared with the unaffected side (middle grey column) (FCR: 19 patients, $P<0.01$; Sol: 17 patients, $P<0.002$) or HC (open column) (FCR: $P<0.0001$; Sol: $P<0.0007$). Individual results (E and F) showed that this asymmetry occurred in most of the patients: 14/19 patients for the FCR (E) and 13/17 patients for the Sol (F). No statistical difference was found between the unaffected side and HC for both FCR ($P=0.45$) (G) and Sol ($P=0.73$) (H).

Presynaptic Ia inhibition
Figure 3, organized as Fig. 2, illustrates the radial- and CPN-induced depression of the FCR (left panels) and Sol (right panels) H reflexes in HC (C and D) and stroke patients (E and F). In HC (C and D), there was no significant asymmetry between the mean values of radial- and CPN-induced depressions of the FCR (C) and Sol (D) H reflexes obtained in both dominant and non-dominant sides: FCR (32 subjects, $P=0.16$) and Sol (39 subjects, $P=0.47$). In stroke patients, mean radial-induced depression of the FCR H reflex (G) was significantly decreased on the affected side with respect to the unaffected side ($P<0.0001$) or HC ($P<0.0001$). Similarly, the mean CPN-induced depression of Sol H reflex (H) was also found to be reduced on the affected side with respect to the unaffected side ($P<0.04$) or to HC ($P<0.0005$). In addition, both the radial- and CPN-induced depressions of the FCR and Sol reflexes on the unaffected side (G and H) were also significantly smaller, although to a lesser extent, than in HC (FCR: $P<0.0006$; Sol: $P<0.04$). Individual results in (E and F) show that asymmetry was observed in most of the patients (35/39 for the FCR and 21/29 for the Sol). Overall, these results suggest that the impairment of presynaptic Ia inhibition behaves similarly in the upper and lower limbs. However, note for discussion that reduced presynaptic Ia inhibition is more marked at cervical (G) than at lumbar (H) segments.

Is spasticity related to impaired efficacy of presynaptic mechanisms?
In a second set of experiments, we hypothesized that the pathophysiology of spasticity could be related to the impairment of the efficacy of presynaptic mechanisms. Since several previous studies failed to demonstrate any significant relationship between the impairment of a given spinal mechanism and the exaggeration of the stretch reflex, probably because of the small number of patients included (see Pierrot-Deseilligny and Burke, 2005), we extended the criteria of inclusion for these experiments by including an additional group of 18 patients suffering from bilateral lesions (see Methods section). In Fig. 4 (A–B and E–F), we compared the mean values of the amount of post-activation depression and that of the presynaptic Ia inhibition at FCR and Sol levels on the affected side of stroke patients (dark grey columns) in two groups of patients: (i) without spasticity (Ashworth’s score = 1); (ii) with spasticity (Ashworth’s scores 2–5). To explore the effect of spasticity within these two groups of patients, we computed a two-way ANOVA for each presynaptic mechanism with factors SPASTICITY (absent versus present) and MUSCLE (FCR versus Sol). ANOVA revealed a significant effect for main factor SPASTICITY ($F=17.11$; $P<0.0001$) for the post-activation depression but not for the presynaptic Ia inhibition.
Post hoc analysis revealed that the post-activation depression is reduced in spastic group patients when compared to the non-spastic one (FCR: \( P < 0.0001 \); Sol: \( P < 0.0001 \)) but not in the non-spastic one (FCR: \( P = 0.29 \); Sol: \( P = 0.63 \)), whereas reduced presynaptic Ia inhibition (Fig. 4A and B) occurred in both groups (Spastic patients: radial-induced depression of FCR H reflex: \( P < 0.0001 \); CPN-induced depression of Sol H reflex: \( P < 0.0001 \); Non-spastic patients: radial-induced...
depression of FCR H reflex: $P < 0.0001$; CPN-induced depression of Sol H reflex: $P < 0.008$). Overall, these results suggest a putative relationship between diminished post-activation depression and the severity of spasticity, and exclude the relationship between presynaptic Ia inhibition and spasticity.

To further investigate the relationship between presynaptic mechanisms and spasticity, we divided the spastic patients into various groups according to the degree of spasticity they expressed. Due to the limited number of patients exhibiting high Ashworth’s scores, patients with scores 4 and 5 were pooled (see Methods section and Fig. 1). Both the means values of the amount of post-activation depression and those of the amount of presynaptic Ia inhibition assessed on the affected side of stroke patients (black triangles) are plotted against the severity of spasticity (Fig. 5). Spearman’s correlation coefficient revealed a significant positive correlation between the reduced post-activation depression (indicated by an increase of the $2/8\text{ s}$ ratio) and the severity of the spasticity for both FCR ($r = 0.57$; $P < 0.0008$) and Sol ($r = 0.69$; $P < 0.0002$) motor nuclei; in other words, the larger diminished post-activation depression of FCR H reflex: $P < 0.0001$; CPN-induced depression of Sol H reflex: $P < 0.008$). Overall, these results suggest a putative relationship between diminished post-activation depression and the severity of spasticity, and exclude the relationship between presynaptic Ia inhibition and spasticity.

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depression, the greater degree of spasticity expressed by the patients. In striking contrast, both radial-induced depression of the FCR H reflex \( (r = 0.26; \quad P = 0.07) \) and CPN-induced depression of the Sol H reflex \( (r = 0.05; \quad P = 0.86) \) were not correlated to the intensity of spasticity.

**Time courses of changes of presynaptic mechanisms following stroke**

**Presynaptic Ia inhibition**

Figure 4C and D displays the amounts of presynaptic Ia inhibition for the FCR (C) and Sol (D) muscle in 28 acute (16 FCR, 12 Sol) and 36 chronic (23 FCR, 13 Sol) monohemispheric stroke patients. To explore within-patients effects, we computed a separate three-factorial ANOVA with factors GROUP (acute versus chronic), MUSCLE (FCR versus Sol) and SIDE (affected versus non-affected). ANOVA revealed only a prominent main effect of factor SIDE \( (F = 17.86; \quad P < 0.0001) \), caused by the overall decrease of presynaptic Ia inhibition on the affected side with respect to the unaffected one. In addition, there was a significant interaction of SIDE x GROUP \( (F = 4.81; \quad P < 0.03) \), providing statistical evidence that the side-dependant changes of presynaptic Ia inhibition differed between the acute and chronic patients.

To explore within-side effects, we computed separate two-factorial ANOVA for each side with GROUP (acute versus chronic) and MUSCLE (FCR versus Sol).

On the unaffected side, ANOVA showed a main effect for factor GROUP \( (F = 6.89; \quad P < 0.01) \). Post hoc analysis revealed that presynaptic Ia inhibition is impaired in acute group when compared to chronic one \( (P < 0.01) \). Likewise, the difference between the unaffected side of chronic patients and HC vanished. Actually, comparisons of measurements between patients and HC revealed that decreased presynaptic Ia inhibition occurs in acute patients but not in chronic ones with respect to HC [radial-induced depression of FCR H reflex \( (P < 0.0002 \text{ in acute and } P = 0.42 \text{ in chronic patients}) \); CPN-induced depression of Sol H reflex \( (P < 0.02 \text{ in acute and } P = 0.89 \text{ in chronic patients}) \)]. On the whole, these results suggest time-linked changes of presynaptic Ia inhibition on the unaffected side of stroke patients.

On the contrary, on the affected side, none of the factors tested were significant suggesting an absence of time-linked changes of presynaptic Ia inhibition on this side.

**Post-activation depression**

Sixteen acute patients (eight FCR and eight Sol) and 17 chronic patients (nine FCR and eight Sol) were enrolled in this set of experiment. As we previously reported a significant positive correlation between the diminished post-activation depression on the affected side and the severity of the spasticity (Fig. 5A and B), we computed separate analysis for each side.

On the affected side, we computed an ANCOVA with factors GROUP (acute versus chronic), MUSCLE (FCR versus Sol) and SPASTICITY (absent versus present) as covariate. 5/16 acute stroke patients expressed spasticity versus 15/17 of the chronic patients. ANCOVA revealed no significant effect either for factor GROUP \( (F = 0.0004; \quad P < 0.98) \) or for factor MUSCLE \( (F = 0.38; \quad P = 0.54) \) but a significant effect of the covariate SPASTICITY \( (F = 13.47; \quad P < 0.001) \) without any significant interaction.

On the unaffected side of stroke patients we computed a two-way ANOVA with factors GROUP (acute versus chronic) and MUSCLE (FCR versus Sol). None of the factors tested were statistically significant.

Analysis of the results does not allow us to draw any conclusion in regards to the time course of changes of post-activation depression after stroke.

**Discussion**

The findings of the present study are: (i) whatever the motor nucleus, presynaptic Ia inhibition was found to be depressed on the affected side and, to a lesser extent, on the unaffected side of stroke patients. Presynaptic Ia inhibition was impaired in both spastic and non-spastic patients when compared to HC; (ii) on the affected side, presynaptic Ia inhibition was impaired in both acute and chronic patients and was not correlated with the severity of spasticity. On the unaffected side, decreased presynaptic Ia inhibition was present in acute patients but not in chronic ones; (iii) whatever the motor nucleus, post-activation depression was found to be depressed on the affected side, but not on the unaffected side of stroke patients and impaired only in spastic patients when compared to HC; (iv) a significant positive correlation was found between the diminished post-activation depression and the severity of spasticity.

**Presynaptic Ia inhibition**

**Affected side: presynaptic Ia inhibition is decreased at cervical and lumbar levels both in acute and chronic patients**

In the upper limb, using the same methodology, results of the previous studies reported all an impairment of the efficacy of the presynaptic inhibition of FCR Ia terminals on the affected side in stroke patients (Nakashima et al., 1989; Artieda et al., 1991; Aymard et al., 2000). Our results are in full accordance with these previous reports and suggest a decrease of presynaptic inhibition of FCR Ia terminals following the loss of corticofugal drive. In the lower limb, conflicting results have been reported in the literature since CPN-induced inhibition of Sol H reflexes was found significantly impaired (Kagamihara and Masakado, 2005) or contradictory not (Aymard et al., 2000) on the affected leg of patients with hemiplegia with respect to HC. However, Aymard et al. (2000) noted that the CPN-induced depression of the Sol H reflex was slightly smaller on both legs of patients when compared to HC, even if the difference
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failed to reach significance (see Fig. 5 in Aymard et al., 2000). We suggest that the small sample of patients they recruited (11) might be responsible for failing to reveal any significant difference. Thus, the significant depression of CPN-induced inhibition of Sol H reflex we reported here on 29 patients strengthens data reported by Kagamihara and Masakado (2005) and did not contradict the study of Aymard et al. (2000).

A similar reduction of presynaptic Ia inhibition following brain lesions at both cervical and lumbar levels may seem surprising taking into account results obtained in animals and healthy human subjects. Indeed, Meunier and Pierrot-Desesilligny (1998) have described a facilitatory corticospinal control on cervical PAD interneurones and an inhibitory corticospinal control on lumbar PAD interneurones. Presynaptic inhibition of Sol Ia terminals markedly decreases at the onset of a voluntary contraction (Pierrot-Deseilligny, 1997; Meunier and Pierrot-Desesilligny, 1998) which implies a tonic control of PAD interneurones at rest. Such a tonic control has been described in cats with spinal transection and after administration of DOPA (Anden et al., 1966). Thus, in the present investigation, if the corticospinal control was normally exerted tonically, corticofugal lesions would be expected to decrease presynaptic inhibition of FCR Ia terminals and to reinforce presynaptic inhibition of Sol Ia terminals.

In the cat hind limb, the main descending control on PAD interneurones mediating presynaptic Ia inhibition is depression, i.e. it decreases PAD excitability and switches off presynaptic inhibition. Last-order PAD interneurones are tonically and strongly inhibited from different reticulospinal pathways (Rudomin and Schmidt, 1999) as revealed by the dramatic increase of excitability of PAD interneurones following the suppression of this strong control after spinalization in decerebrate animals. Moreover, these brainstem structures responsible of this tonic depressive effect on presynaptic inhibition receive a descending inhibitory control from higher structures which is in keeping with the absence of presynaptic inhibition in decerebrate animal. Thus, the most-likely mechanism that contributes to the tonic level of presynaptic inhibition at rest is tonic inhibition from higher centers of the brainstem structures through which reticulospinal pathways maintain tonic inhibition of last-order PAD interneurones (Rudomin and Schmidt, 1999).

In relation to these findings, the simplest explanation of our results lies on the observation that reduced presynaptic inhibition of FCR Ia terminals was more marked than that of Sol Ia terminals (compare dark grey and open columns on Fig. 3G versus H). At the cervical segment, the direct loss of the facilitatory corticospinal control of PAD interneurones combined with a mechanism of disinhibition, due to the suppression of the inhibitory control from higher structures to inhibitory brainstem structures, may explain the drastic reduced radial-induced depression of FCR H reflex after stroke. At the lumbar segment, the suppression of the inhibitory control of PAD interneurones by brainstem structures through a similar mechanism of disinhibition would be expected to depress the presynaptic inhibition of Sol Ia terminals, whereas the loss of the inhibitory corticospinal control of PAD interneurones would be expected to have an opposite effect. Therefore, the net results of the two opposite effects may explain the discrete depression of presynaptic inhibition of Sol Ia terminals. Such a functional balance may also be responsible for masking non-consistent changes reported in previous studies on a smaller sample of patients using either the same experimental method (Aymard et al., 2000) or the heteronymous monosynaptic Ia facilitation (Faist et al., 1994) to test presynaptic Ia inhibition.

Whatever the spinal segment considered (Fig. 4C and D), presynaptic inhibition was similarly depressed on the affected side of both acute and chronic stroke patients with respect to HC. These findings suggest that the cortical lesion disrupts immediately the supraspinal influences (i.e. corticospinal and brainstem pathways) over segmental PAD interneurones and switches off presynaptic inhibition. In this respect, one patient, who was enrolled as soon as 6 days after stroke occurred, exhibited a dramatic reduction of radial-induced depression of FCR H reflex (92.93%). Moreover, presynaptic Ia inhibition was reduced in most of the acute patients: 14/16 at the cervical level, 9/12 at the lumbar segment.

Unaffected side: Presynaptic Ia inhibition is decreased at cervical and lumbar levels in acute but not in chronic patients

Presynaptic Ia inhibition of the H reflex is decreased on the unaffected side in acute stroke patients, though to a lesser extent than on the affected side. Abnormal transmission in some spinal pathways has been described on the apparent unaffected side of patients with a unilateral focal lesion (see Pierrrot-Desesilligny and Burke, 2005). Slight weakness has also been reported on the unaffected upper limb, possibly reflecting ipsilateral corticofugal projections (Gandevia, 1993). In this respect, disturbed supraspinal influence on PAD interneurones ipsilateral to the lesion might result in an immediate reduction of presynaptic inhibition as observed on the unaffected side of acute stroke patients. The restoration of presynaptic inhibition in the unaffected side of chronic patients may be due to a compensation originating from the contralateral (unaffected) hemisphere or to the fact that the loss of supraspinal influences on this set of interneurones might be counteracted by the normal activity induced-plastic changes.

Post-activation depression

Several previous studies have demonstrated, in resting state, that post-activation depression is decreased on the affected side of spastic patients (Nielsen et al., 1993, 1995; Aymard et al., 2000; Schindler-Ivens and Shields, 2000; Masakado et al., 2005; Grey et al., 2008) but not depressed on their...
unaffected side (Aymard et al., 2000, Fig. 2G and H). The present investigation confirms these previous results and brings new findings suggesting that this mechanism may be a contributing factor in the expression of spasticity. Even though, as highlighted by Nielsen et al. (2007), a correlation by itself cannot be used as a proof of causality, we reported here, for the first time, a significant correlation between diminished post-activation depression and the severity of spasticity (graded using Ashworth’s scale) at both cervical and lumbar segments (Fig. 5A and B). However, we failed to reveal any significant difference between acute and chronic stroke patients with SPASTICITY as covariate, so it is not possible to draw any conclusion as regards a potential link between the time course of the impairment of post-activation depression and that of the development of spasticity in stroke patients. This issue should be answered by conducting longitudinal studies. Nevertheless, several studies in animals revealed that impaired post-activation depression paralleled the time course of the development of spasticity. In spinal lesioned rats, the impairment of post-activation depression was shown to occur not immediately after the lesion but only 3 months after the lesion in a activation depression was shown to occur not immediately

spasticity. In spinal lesioned rats, the impairment of post-activation depression and the severity of spasticity (graded using Ashworth’s scale) at both cervical and lumbar segments (Fig. 5A and B). However, we failed to reveal any significant difference between acute and chronic stroke patients with SPASTICITY as covariate, so it is not possible to draw any conclusion as regards a potential link between the time course of the impairment of post-activation depression and that of the development of spasticity in stroke patients. This issue should be answered by conducting longitudinal studies. Nevertheless, several studies in animals revealed that impaired post-activation depression paralleled the time course of the development of spasticity. In spinal lesioned rats, the impairment of post-activation depression was shown to occur not immediately after the lesion but only 3 months after the lesion in a model of transsection (Skinner et al., 1996) or from 28th day after the lesion in a model of midthoracic contusion (Thompson et al., 1992). In humans, a decreased post-activation depression of Sol reflexes was also observed in chronic spinal cord injured patients when compared with acute ones, suggesting that the attenuation of post-activation depression occurs gradually over time (Calancie et al., 1993; Schindlers-Ivens and Schields, 2000). Importantly, a longitudinal study of one patient with spinal cord injury showed that the reduction of post-activation depression developed with the transition from flaccid to spastic paralysis (Schindlers-Ivens and Schields, 2000). Overall, these findings suggest that development of adaptative changes in the efficacy of the Ia fibre–motoneurone synapse follows the changes in activity of Ia fibers and motoneurones associated with the impaired motor command. Moreover, contrary to other electrophysiological changes explored (see Introduction section; Fig. 2G and H), post-activation depression is unchanged on the unaffected side of stroke patients and to our knowledge, impaired post-activation depression has never been described for other clinical dysfunctions than spasticity. In respect to a more clinical point of view (see below), it is interesting to note that post-activation depression has been recently found to be correlated with the absence/presence of clonus (Masakado et al., 2005).

Possible interactions between presynaptic inhibition and post-activation depression

Even though this study provides arguments suggesting that changes in presynaptic Ia inhibition does not play a major role in the development of spasticity, the possible interaction between decreased presynaptic Ia inhibition and decreased post-activation depression has to be taken into account since an interaction between presynaptic Ia inhibition, (thought to be mediated by GABA), and post-activation depression has been suggested from physiological and pharmacological studies in animals. Indeed, Davies et al. (1985a, b) showed in the cat spinal lumbar cord that post-activation depression is altered by administration of benzodiazepines and that this effect is linked to the prolongation of the primary afferent depolarization. In other words, changes in presynaptic inhibition result in changes in post-activation depression. In 2002, Enriquez-Denton et al. studied in the cat spinal cord the interaction between repetitive activation of peripheral afferents and presynaptic Ia inhibition and suggested that afferent activity may decrease the efficiency or presynaptic inhibition. In 2008, Barrière et al. have investigated the modulation by serotonin, dopamine and noradrenaline, of the short-term post-activation depression at the sensory afferent α-motoneurone synapses in the neonatal rat spinal cord. They showed that the different modulation profiles observed with the amines are partly due to GABAAergic interneurone activity. In this respect, it is interesting to note that Cardona and Rudomin (1983) described that activation of brainstem serotoninergic pathways decreases post-activation depression in frog spinal cord. Although the findings in the neonatal rat spinal cord cannot be transposed to humans without caution, these results suggest that changes in presynaptic inhibition may influence post-activation depression. In humans, Rudell et al. (1988) reported a case of exacerbation of spasticity in an amyotrophic lateral sclerosis patient following dextroamphetamine treatment suggesting that this may be due to the fact that the patient was more susceptible to the dopaminergic motor stimulatory action of dextroamphetamine.

Recently in healthy subjects, Lamy et al. (2005) studied the effects of repetitive stimulation (0.16 and 1 Hz) of group I afferents onto the amount of presynaptic inhibition at FCR and Sol levels. They showed that the amount of presynaptic inhibition was enhanced at high stimulus rate. This result in humans confirms previous results obtained in the cat (Hammar et al., 2002) indicating that post-activation depression depends on the type of group I afferents and/or on the target neurones. Thus, to go further in the possible interaction between changes in presynaptic inhibition and changes in post-activation depression in the development of spasticity, the effects of repetitive stimulation of group I afferents onto presynaptic Ia inhibition, have to be performed in spastic stroke subjects.

Pathophysiological significance of presynaptic disorders for spasticity

Spasticity is part of the upper motor neurone syndrom which is of special interest for both clinicians and researchers, since it is accessible for drug therapy. However, its definition is still debated among clinicians and physiologists. In the Introduction section, we defined spasticity following Lance (1980) as 'a motor disorder characterized by a velocity
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dependent increase in tonic stretch reflex "muscle tone" with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex. However, clonus, spasms and hyperreflexia are also often included in clinical definition of spasticity (Pierrot-Deseilligny and Burke, 2005; Nielsen et al., 2007). Even though the definition of spasticity is restricted to that of Lance, abnormality in anyone of the spinal mechanisms controlling the excitability of the stretch reflex may produce a hyperexcitability of the stretch reflex. Briefly, as summarized by Pierrot-Deseilligny and Burke (2005) and Nielsen et al. (2007), in addition to decreased presynaptic Ia inhibition or post-activation depression, hyperexcitability of α-motoneurones (including plateau-potentials), increased fusimotor activity, increased oligosynaptic propriospinally-mediated group I excitation, increased group II excitation, increased Ib facilitation, decreased reciprocal and non-reciprocal inhibition, decreased recurrent inhibition, may theoretically induced spasticity. Moreover, it must be kept in minds that spasticity takes time to develop and thus could be due both to alterations of supraspinal controls caused by the cerebral lesion and to plastic changes at spinal cord level, secondary to the loss of the supraspinal drive disrupted by the cerebral lesions. Finally several studies suggest that increased muscle tone in some patients are mainly due to changes in the intrinsic properties of muscles (Dietz et al., 1981).

During the last 40 years, these possible mechanisms have been explored both in animals and humans. To summarize, up to now in stroke patients at rest, pathophysiological changes in post-synaptic effects has been reported for reciprocal Ia inhibition, Ib pathways, group II pathways, propriospinal pathways. Possible hyperexcitability of α-motoneurones is likely but relies only on indirect findings (increased F-wave and H reflexes). Contrary to what was hypothesized in the 1960s, in stroke patients at rest, there is no evidence for changes in fusimotor activity or recurrent inhibition (for references, see Pierrot-Deseilligny and Burke, 2005).

As far as presynaptic mechanisms (presynaptic Ia inhibition and post-activation depression) are concerned, previous experiments (see Introduction section) reported that these mechanisms are impaired in stroke patients at rest, but failed to report a positive correlation between their dysfunctions and the severity of spasticity, despite the fact that a decrease in presynaptic Ia inhibition and/or a decrease in post-activation depression will theoretically result in an exaggeration of the monosynaptic reflexes. Although we confirm that presynaptic Ia inhibition is reduced in stroke patients, our results suggest that reduced presynaptic Ia inhibition by itself plays a limited, or no, physiopathological role in the spasticity as assessed under resting conditions: (i) there is no correlation between the extent to which radial- and CPN-induced depressions of the FCR and Sol H reflexes (Fig. 5C and D) are decreased and the severity of spasticity, (ii) presynaptic Ia inhibition is reduced, although to a lesser extent, on the unaffected side of acute stroke patient in the absence of any other evidence to suggest spasticity or motor impairment in the corresponding muscles, (iii) even if presynaptic inhibition appears to be impaired in most of spastic patients, it is also reduced in patients with movement disorders other than spasticity such as Parkinson's disease (Lelli et al., 1991) or several kinds of dystonia related to lesions of the contralateral basal ganglia (Nakashima et al., 1989; Panizza et al., 1990) and (iv) the finding that presynaptic Ia inhibition has only a limited effect on the reflex responses to abrupt stretch makes it unlikely that a decrease could contribute significantly to the clinically exaggerated stretch reflex (Pierrot-Deseilligny and Burke, 2005).

On the contrary, for post-activation depression, the present investigation confirms and further demonstrates that this mechanism may be a contributing factor in the expression of spasticity by demonstrating a positive correlation between diminished post-activation depression and the severity of spasticity. Several lines of evidence suggest that plastic changes in the efficacy of the Ia fibre–motoneurone synapse follow the changes in activity of firing motoneurones and Ia fibres resulting from the impairment of the motor command. Contrary to animal decerebrate rigidity, which is present as anesthesia wears off, human spasticity cannot be considered as an immediate consequence of the CNS lesion, since it progresses during weeks or months after the causal lesion. This gives time for synaptic rearrangements to occur at the spinal level. Thus, it is highly probable that the lack of activity due to the motor impairment contributes to the resistance to stretch characterizing spasticity. In this respect, synaptic efficacy of primary afferents have been shown to be up or downregulated by disuse or use of synapses (Gallego et al., 1979) and spinal use-dependant plasticity of post-activation depression has been reported after a single cycling session (Meunier et al., 2007). These findings suggest that development of adaptive changes in the efficacy of the Ia fibre–motoneurone synapse follows the changes in activity of Ia fibres and motoneurones associated with the impaired motor command.

Whatever its origin, impaired post-activation depression observed in stroke patients would enhance the synaptic efficacy of the trains of Ia volley in firing motoneurones and might therefore be responsible for stretch reflex exaggeration that characterizes spasticity. Therefore, decrease in post-activation depression likely contributes to the exaggeration of monosynaptic reflexes and may contribute to the appearance of a stretch reflex in resting muscles during voluntary antagonistic contractions. Although the contribution of spasticity to motor impairment in stroke patients is still a debated question (for references, see Pierrot-Deseilligny and Burke, 2005), it is likely that a voluntary movement stretching a spastic muscle may produce a reflex in the antagonistic muscle that would oppose the voluntary movement. In this respect, it has been recently reported (Kamper et al., 2003) that exaggerated stretch reflexes in the
fnger fexors contribute to the impairment of fnger extension in stroke patients.

Supplementary material
Supplementary material is available at Brain online.

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