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Pre- and Post-Alpha Motoneuronal Control of the Soleus H-Reflex during Sinusoidal Hip Movements in Human Spinal Cord Injury

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Abstract

The aim of this study was to establish the contribution of hip-mediated sensory feedback to spinal interneuronal circuits during dynamic conditions in people with incomplete spinal cord injury (SCI). Specifically, we investigated the effects of synergistic and antagonistic group I afferents on the soleus H-reflex during imposed sinusoidal hip movements. The soleus H-reflex was conditioned by stimulating the common peroneal nerve (CPN) at short (2, 3, and 4 ms) and long (80, 100, and 120 ms) conditioning test (C-T) intervals to assess the reciprocal and pre-synaptic inhibition of the soleus H-reflex, respectively. The soleus H-reflex was also conditioned by medial gastrocnemius (MG) nerve stimulation at C-T intervals ranging from 4 to 7 ms to assess changes in autogenic Ib inhibition during hip movement. Sinusoidal hip movements were imposed to the right hip joint at 0.2 Hz by the Biodex system while subjects were supine. The effects of sinusoidal hip movement on five leg muscles along with hip, knee, and ankle joint torques were also established during sensorimotor conditioning of the reflex. Phase-dependent modulation of antagonistic and synergistic muscle afferents was present during hip movement, with the reciprocal, pre-synaptic, and Ib inhibition to be significantly reduced during hip extension and reinforced during hip flexion. Reflexive muscle and joint torque responses – induced by the hip movement – were entrained to specific phases of hip movement. This study provides evidence that hip-mediated input acts as a controlling signal of pre- and post-alpha motoneuronal control of the soleus H-reflex. The expression of these spinal interneuronal circuits during imposed sinusoidal hip movements is discussed with respect to motor recovery in humans after SCI.

Keywords: Hip movement, Reciprocal pre-synaptic autogenic, inhibition, Paraplegia, Rehabilitation. Spasms

Abbreviations: CPN, common peroneal nerve; EMG, electromyographic; $Ho^{homonymous}$, control soleus; H-reflex recorded during hip; flexion or extension without any conditioning stimulation and used to normalize the size of the conditioned reflexes recorded in

the same orientation of hip movement; Ho, control soleus H-reflex recorded with subjects supine; MG, medial gastrocnemius; MH, medial hamstrings; PTN, posterior tibial nerve; SCI, spinal cord injury; SEM, standard error of mean; SOL, soleus; TA, tibialis anterior; VL, vastus lateralis; VM, vastus medialis

1. Introduction

The modulation of spinal inhibitory pathways is likely to be important to locomotor control in people with spinal cord injury (SCI). In particular, it has been suggested that impaired modulation of spinal inhibitory control systems is associated with the pathological expression of movement and muscle tone in human SCI (Hultborn, 2003; Pierrot-Deseilligny and Mazevet, 2000). For example, the amount of reciprocal inhibition appears to be correlated with the amount of motor recovery (Okuma et al., 2002), and its loss emerges with the appearance of spasticity following injury (Crone et al., 2003). Modulation of Ia input, presumably through pre-synaptic mechanisms, is also diminished under specific static (Faist et al., 1994; Morita et al., 2001) and dynamic (Yang and Whelan, 1993) conditions in people with SCI. Similarly, autogenic inhibition is reduced by SCI (Delwaide and Oliver, 1988). These effects on spinal inhibitory pathways could further exacerbate the devastating effects of paralysis on functional movements, such as walking, leading to spastic gait (Fung and Barbeau, 1989).

Stretch-sensitive afferents from the hip flexors can reset or entrain the locomotor rhythm in spinal or decerebrate cats (Andersson and Grillner, 1983; Kriellaars et al., 1994; Hiebert et al., 1996; Lam and Pearson, 2001), emphasizing the impact of this sensory feedback to walking. Sensory feedback from the hip also appears to be important to the generation of locomotor muscle activity in human SCI during assisted walking (Dietz et al., 1998, 2002), and imposed sinusoidal hip motion induces locomotor-like muscle activity throughout the legs in supine SCI subjects (Steldt and Schmit, 2004). These observations are consistent with the involuntary alternating stepping-like movements in the lower extremities that have been reported in an SCI patient lying supine with extended hips (Calancie et al., 1994).

Akin to the role of hip afferents in triggering locomotor reflexes, hip proprioceptors also affect soleus H-reflexes, with reflex facilitation and inhibition to be observed with hip extended and flexed respectively in both neurologically intact and SCI individuals (Knikou and Rymer, 2002a,b). Further, actions of hip proprioceptors affect the excitability

of spinal inhibitory control systems in spinal intact subjects (Knikou and Rymer, 2002a; Knikou, 2006b); however, a similar hip-induced modulation of the inhibitory pathways is not observed in subjects with SCI (Knikou, 2005).

The objective of the current study was to quantify the modulation of inhibitory reflex pathways by actions of dynamic hip proprioceptors in people with SCI. Reciprocal inhibition, mediated via the muscle spindle group Ia afferents of the antagonists, can be assessed by conditioning the soleus H-reflex with a low strength electrical stimulus to the common peroneal nerve (CPN) (Crone et al., 1987; Crone, 1993). Further, pre-synaptic inhibition of the soleus H-reflex can also be measured using a conditioning volley applied to the CPN 60–120 ms before the tibial nerve stimulus (Crone and Nielsen, 1994). The ensuing reflex depression is attributed to pre-synaptic inhibition of Ia afferents (Katz, 1999). Autogenic inhibition of the soleus H-reflex can be induced when the medial gastrocnemius (MG) nerve is stimulated first, possibly through group Ib autogenic inhibitory pathways (Pierrot-Deseilligny et al., 1979).

Modulation of reciprocal, pre-synaptic, and autogenic inhibition were quantified in the current study by examining targeted H-reflex conditioning during imposed movements of the hip in a group of subjects with sensory motor incomplete SCI. The underlying spastic reflex effects associated with imposed hip movements were monitored during testing using measurements of ongoing EMG and joint torque responses at the hip, knee, and ankle. Some of the findings reported here have been presented in abstract form (Chaudhuri et al., 2006).

2. Results

2.1. Effects of imposed sinusoidal hip movements on soleus H-reflex combined with CPN stimulation

Excitation of flexor group I afferents induced TA responses were consistent during all test conditions and subjects tested. Fig. 1A illustrates the effects of CPN stimulation on TA activity in two subjects (S7 and S11) as the hip was extended and flexed. The TA H-reflex was of similar magnitude in both subjects during hip flexion and extension, whereas the M-waves remained relatively constant for both movement conditions. The average size of the TA M-wave, measured as the area under the rectified curve, during hip flexion and extension for all C-T intervals in subject 7 is illustrated in Fig. 1B. Across C-T intervals and hip movement direction, the M-wave size was not statistically

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significant different (P = 0.981, repeated measures ANOVA), a phenomenon that was observed across subjects.

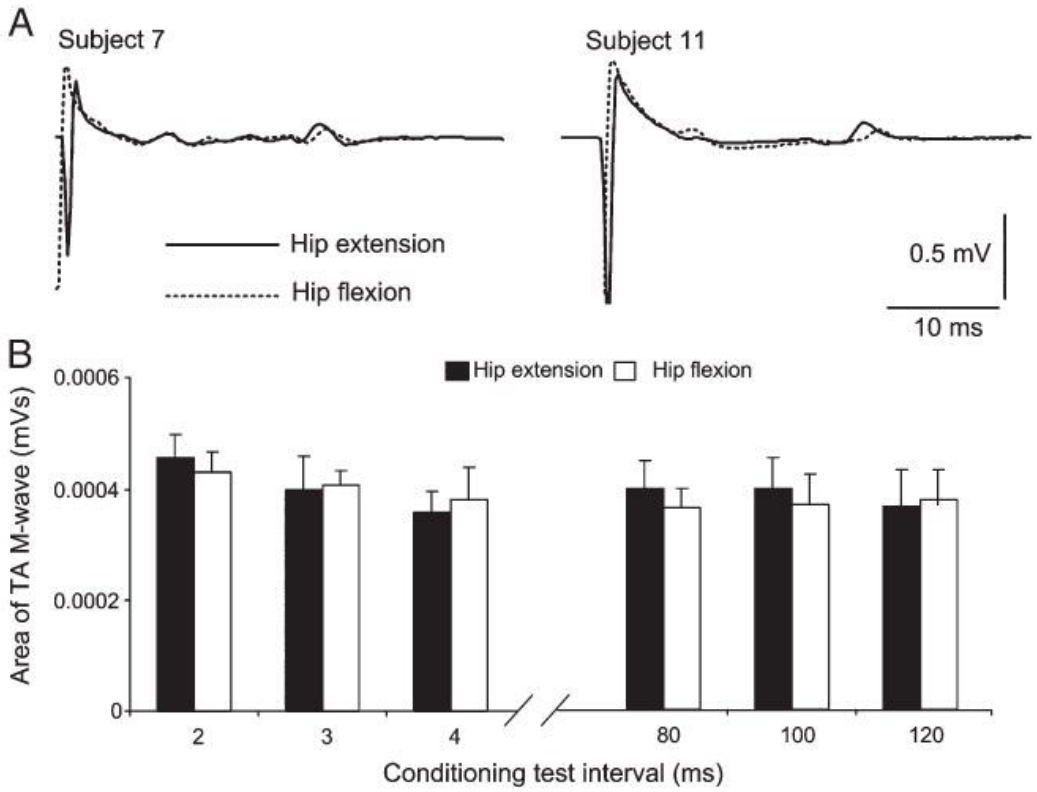

Fig. 1 (A) Tibialis anterior (TA) activity during sinusoidal hip movements. Representative EMG activity in the TA muscle is shown for two subjects (S7 and S11) when the stimulus to the common peroneal nerve (CPN) was delivered with the hip in mid-extension and mid-flexion. Note the similar sizes of the M-waves during hip movement. (B) Average (n = 10) size of TA M-wave in subject 7 during hip flexion and extension for all C-T intervals tested. No statistically significant difference was found between the M-waves recorded during hip flexion and extension across C-T intervals tested.

CPN stimulation during imposed sinusoidal hip movements resulted in significant changes on the soleus H-reflex size. Fig. 2 shows the effects of CPN stimulation on the average soleus H-reflex at the C-T interval of 100 ms with the hip in mid-extension and mid-flexion (data are from subject 11). The soleus H-reflex was significantly depressed at this interval during hip extension. Conversely, the CPN stimulation at the 100-ms C-T interval during hip flexion facilitated the H-reflex, an effect that was also observed across the population.

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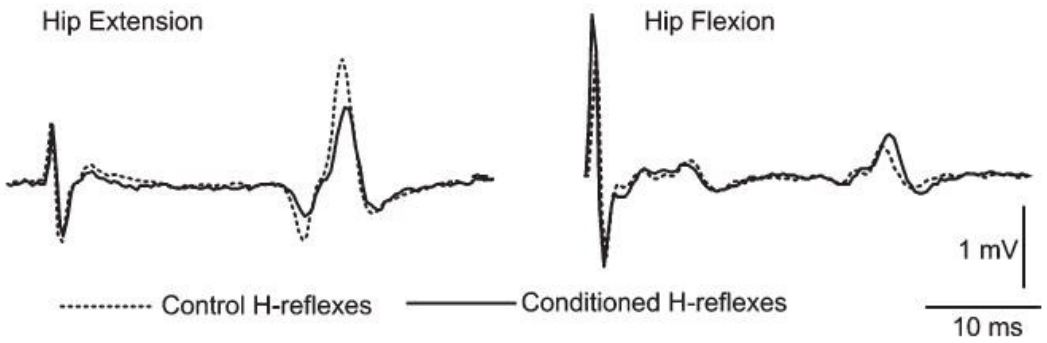

Fig. 2 The average H-reflex (unrectified) recorded under control conditions (dotted lines) and during conditioning of the reflex with CPN stimulation (solid lines) at the conditioning test intervals of 100 ms while the hip was moving in extension and flexion are presented. Note that the reflex modulation occurred without significant changes in the magnitude of the M-wave.

The population data for the conditioned H-reflex following CPN stimulation while the hip moved in flexion and extension are illustrated for all conditioning test (C-T) intervals in Fig. 3A. The conditioned H-reflex reached an overall magnitude of 130 ± 8% and 135 ± 20% of $Ho^{homonymous(1)}$ ($P < 0.05$) as the hip moved in flexion at the C-T intervals of 3 and 4 ms, respectively. In contrast, the soleus H-reflex was depressed during hip extension, being statistically significant only at the C-T interval of 2 ms. CPN stimulation induced similar significant effects on the soleus H-reflex size during imposed sinusoidal hip movements when long C-T intervals (80, 100, and 120 ms) were used. In summary, the conditioned soleus H-reflexes were facilitated during hip flexion and depressed during hip extension (Fig. 3A).

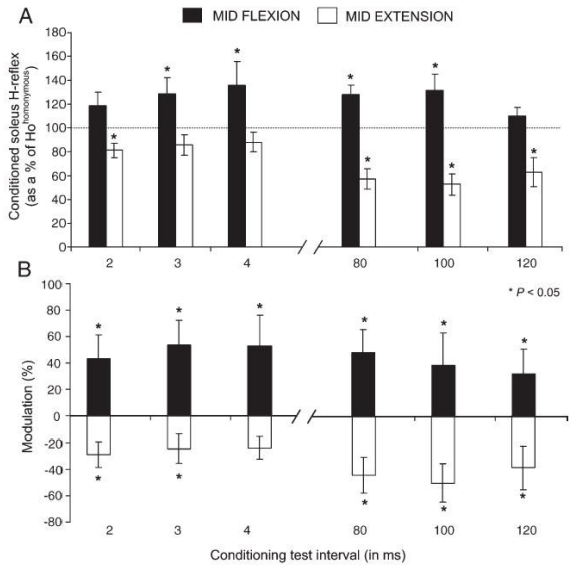

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Fig. 3 (A) Pool data (all subjects tested) of the effects of common peroneal nerve stimulation on the soleus H-reflex at short (2–4 ms) and long (80–120 ms) conditioning test intervals during imposed hip movements. (B) Overall modulation of reciprocal and pre-synaptic inhibition during imposed sinusoidal hip flexion and extension. A decrease in modulation is presented as negative values whereas an increase is shown as positive values. For all cases, the modulation was estimated based on Eq. (1). For both graphs, the error bars designate the SEM and asterisks indicate cases of statistically significant differences ($P < 0.05$).

The modulation of reciprocal Ia (CPN stimulation at short C-T intervals) and pre-synaptic inhibition (CPN stimulation at long C-T intervals) was estimated using Eq. (1) (see Experimental procedures) and depended on the direction of the hip movement. Both reciprocal and pre-synaptic inhibition were decreased during hip extension, whereas hip flexion resulted in potentiation of both inhibitory mechanisms (Fig. 3B). The decrease in modulation of pre-synaptic inhibition shown in Fig. 3B is not presented as an increased H-reflex during hip extension, probably because of differences of $Ho^{homonymous}$ sizes during hip flexion and extension (see Fig. 10C).

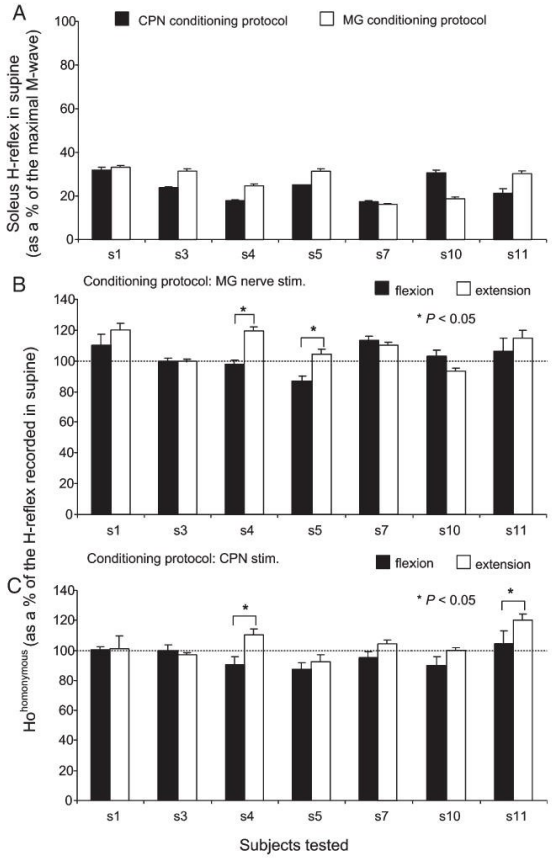

Fig. 10 (A) The average size ($n = 20$) of the soleus H-reflex recorded without any conditioning stimulus with subjects supine as a percentage of the maximal M-wave is

illustrated for both conditioning experimental trials (CPN and MG tests). Soleus H-reflexes ranged from 15% to 35% of the maximal M-wave across subjects. (B, C) The average size of the $Ho^{homonymous}$ reflexes during hip flexion and extension for both conditioning protocols (CPN and MG) are shown as a percentage of the mean size of the soleus H-reflex (without the presence of conditioning stimulus) recorded with subjects supine. Asterisks indicate cases of statistically significant differences of the $Ho^{homonymous}$ reflexes during hip flexion and extension. Note that only in 4 out of 28 cases the $Ho^{homonymous}$ reflex was not of similar size during hip flexion and extension. In all graphs, error bars designate the standard error of the mean, whereas the subject number is denoted on the abscissa.

In this study, the imposed hip movements produced a reflex activation of many muscles throughout the leg, resulting in a phase-dependent pattern of muscle EMGs and joint torques that was qualitatively similar to those observed with more rapid oscillations of the hip (Steldt and Schmit, 2004). The underlying reflex actions produced by the passive hip movements might be directly related to the modulation of pre-synaptic and reciprocal inhibitory pathways with hip movement, and documenting the patterns of underlying reflex activity could interpret the modulation of the inhibitory pathways.

The underlying muscle patterns were generally consistent across all test conditions, whereas the stimulus produced a brief response in some muscles. The normalized activity of all five muscles recorded in each subject (grey lines) and the average (black lines) when the soleus H-reflex was conditioned with CPN stimulation at 2 or 100 ms during hip movement is illustrated in Fig. 4. The SOL and MH displayed the most consistent responses regardless of the stimulus timing, being present at mid-hip extension and flexion, respectively. In contrast, TA, VM, and VL responses coincided mostly with the timing of the stimulus, especially when the peripheral nerves were stimulated with the hip in mid-flexion. Similar muscle response patterns were observed at the short and long C-T intervals tested, indicating that the timing of the conditioning stimulus did not impact the underlying muscle activity.

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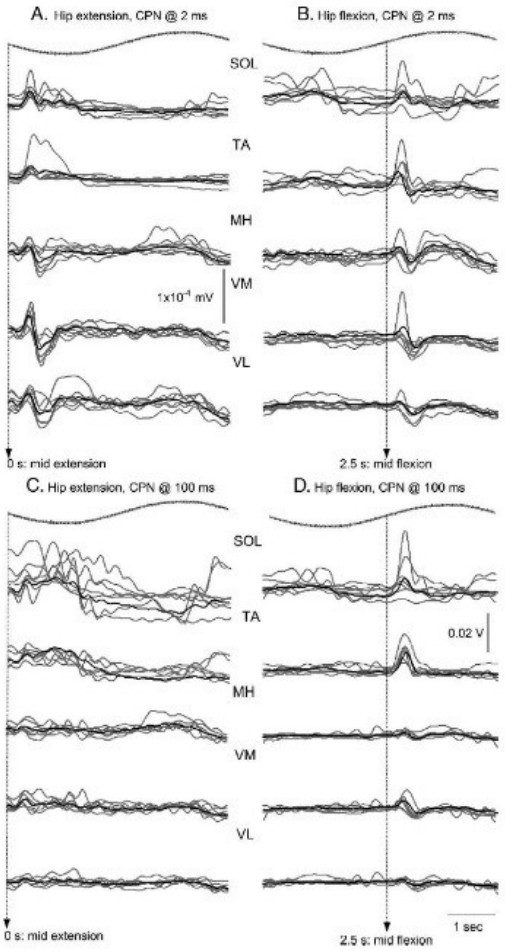

Fig. 4 Normalized average muscle responses during sinusoidal hip extension and flexion when the soleus H-reflex was conditioned by common peroneal nerve stimulation at the conditioning test intervals of 2 ms (A, B) and 100 ms (C, D). The grey lines indicate muscle responses (average of 10 consecutive hip movement cycles) from individual subjects, and the black lines indicate the average of all seven subjects. The top traces of each figure indicate the sinusoidal movement of the hip, whereas the vertical dotted lines identify the position of the hip (0 s for mid-extension, 2.5 s for mid-flexion) during which the soleus H-reflex was conditioned by common peroneal nerve stimulation. It is clear that the SOL, TA, and MH muscle responses occurred independent of the timing of the stimulus, whereas SOL responses were mostly observed during the transition of the leg from flexion to extension.

The stimulus, however, did appear to have an effect on the underlying reflex response to passive hip oscillation in selected cases. Specifically, a diffuse muscle activity was seen in response to stimulation in 4 out of 7 subjects (S3, S7, S10, and S11). A representative example of this unusual oscillatory activity is illustrated in Fig. 5. Figs. 5A and B represent raw and integrated muscle responses, respectively, for three consecutive hip movement cycles (each cycle lasted 5 s) for a single subject (S7). The muscle activity is

from the trial where the soleus H-reflex was conditioned at the C-T interval of 100 ms. This subject showed similar oscillatory activity in all of the conditioning trials, whereas the oscillatory activity in the other subjects was mainly observed in the ankle extensors and flexors and was most prominent with the hip in extension. Fig. 5C illustrates raw muscle activity when extensor spasms were present during sinusoidal hip movements whereas no peripheral nerves were stimulated (data are from S10). The corresponding reflexive (in response to hip movement) joint torques from the hip, knee, and ankle are shown in Fig. 5D. Muscle and torque responses suggest an activation pattern that is consistent with extensor spasms.

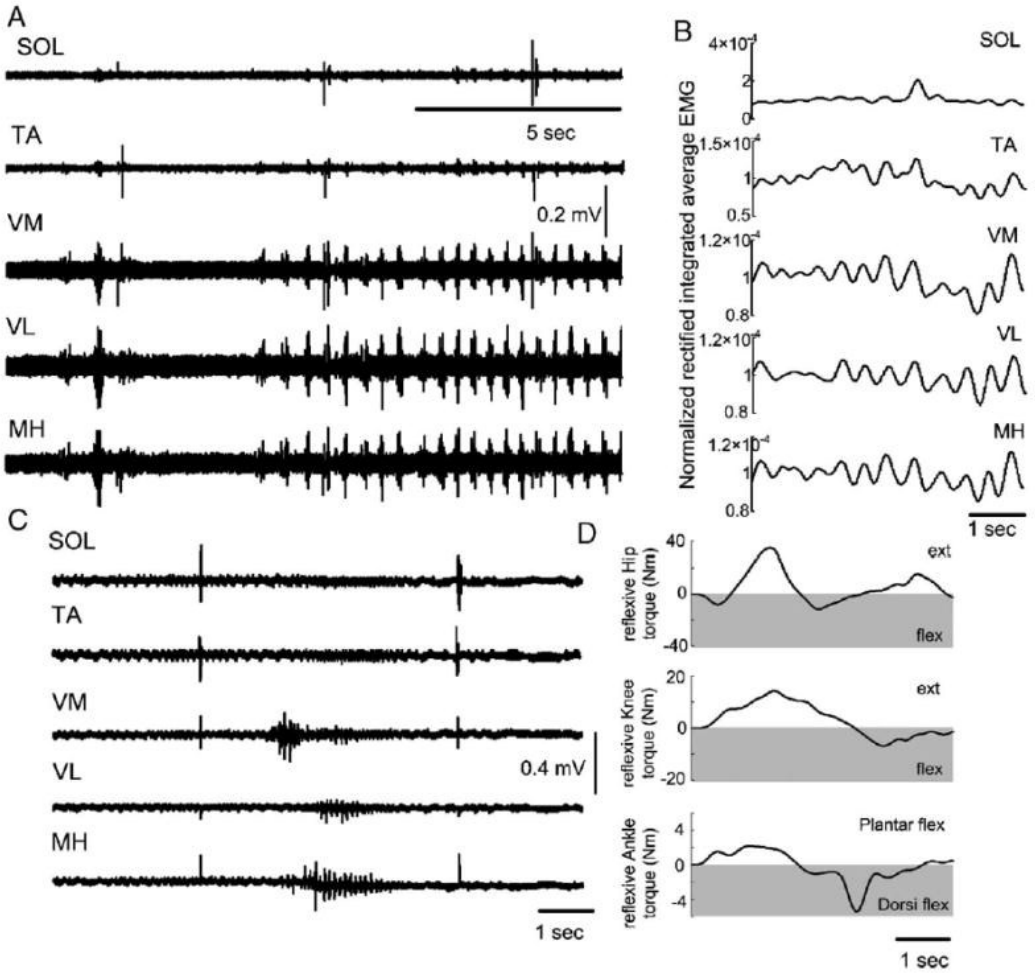

Fig. 5 Oscillatory muscle activity during sinusoidal hip movements. EMG raw data for 3 full cycles of hip movement (A) and the respective full-wave rectified normalized average (10 consecutive hip movement cycles) EMG responses (B). Typical EMG responses are from the trial where the soleus H-reflex was conditioned with common peroneal nerve stimulation at 100 ms C-T interval during hip flexion. It is clear that spasms were initiated by the imposed hip movement. Raw muscle activity recorded during sinusoidal hip movements whereas none of the peripheral nerves were

stimulated, but when extensor spasms were present is illustrated in panel C. For VM, VL, and MH vertical lines in panel C denote Biodex artifacts, whereas for SOL and TA the corresponding peaks are muscle responses that cannot be seen because of the time scale. The associated reflexive hip, knee, and ankle joint torques are presented in panel D.

The reflexive joint torque data also indicated that there was modest, ongoing, multi-joint spastic reflex activity during the hip oscillations. The hip, knee, and ankle reflexive joint torques that were present when the soleus H-reflex was conditioned with CPN stimulation at 2 and 100 ms during hip flexion and extension are illustrated for all subjects in Fig. 6. The bottom traces of Fig. 6 illustrate that the stimulus produced a brief plantar flexion moment at the ankle joint. At mid-flexion, the ankle was transitioning from a plantar flexion to dorsiflexion (or neutral) torque. Conversely, at mid-extension the opposite occurred, with a transition from dorsiflexion (or neutral) to active plantar flexion torque. When the stimulus was applied during extension, this brief torque was masked somewhat by the ongoing spastic plantar flexion torque associated with the reflex response to the imposed hip movement itself.

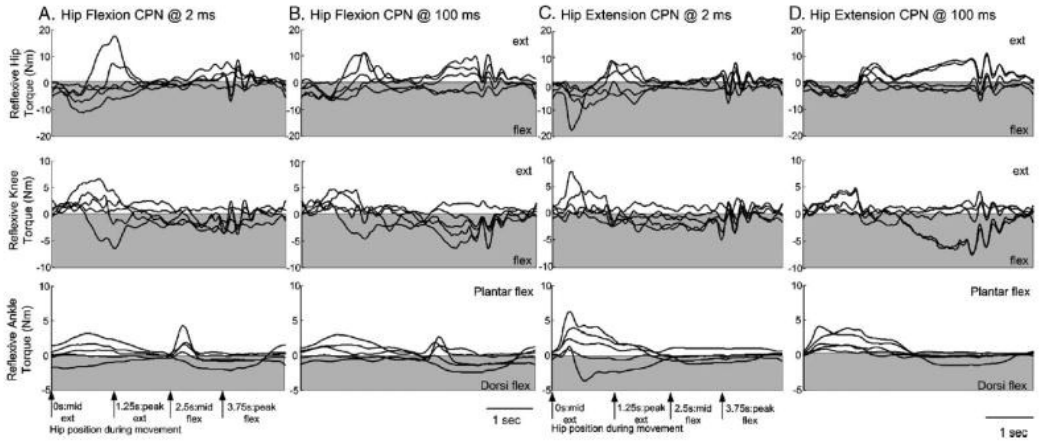

Fig. 6 Reflexive joint torques following excitation of antagonistic muscle afferents due to sinusoidal hip movement. Hip, knee, and ankle reflexive torques (Nm) when the soleus H-reflex was conditioned by common peroneal nerve stimulation at 2 and at 100 ms during hip flexion (A, B) and hip extension (C, D). Each waveform represents the average of 10 consecutive hip movement cycles. Arrows at the bottom of the figures indicate the position of the hip during a hip sinusoidal movement cycle (mid-extension at 0 s, peak extension at 1.25 s, mid-flexion at 2.5 s, and peak flexion at 3.75 s). For extension trials, stimuli were delivered at 0 s and for flexion trials at 2.5 s. Torques above zero designate extension and those below zero designate flexion. Oscillatory flexion/extension joint torques were observed mostly after the hip had passed peak flexion and lasted until the transition phase from flexion to extension. Ankle torques depended largely on the timing of the stimulus, whereas hip and knee joint torques were more complex.

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The hip and knee joint torques showed more complex behavior than the ankle joint. When conditioned reflexes were recorded at short (2 ms) or long (100 ms) C-T intervals during hip flexion (Figs. 6A and B) the hip was transitioning to an extensor torque. The underlying reflex behavior of the hip when the peripheral nerves were stimulated with the hip in mid-extension (Figs. 6C and D) were slightly less consistent with evidence of hip flexion torque during late extension, which reversed to hip extension torque when the direction of the imposed movement was reversed. The knee joint torques generally mirrored the direction of the hip movement, and they were in flexion or extension depending on the timing of the conditioning stimulus and the phase of the hip movement. The oscillatory behavior of the hip and knee torques just before peak flexion might be related to the clonic activity of the MH (see Fig. 4) but are also consistent with spastic muscle activity. It is noteworthy that the oscillatory expression of the hip and knee joint torques was most prominent when the hip had passed mid-flexion and during the transition of the hip from flexion to extension.

2.2. Effects of imposed sinusoidal hip movements on soleus H-reflex combined with MG nerve stimulation

MG nerve stimulation resulted in significant changes on the soleus H-reflex size during imposed sinusoidal hip movements. A summary of all changes of the soleus H-reflex size during hip movement (i.e., flexion and extension) for all C-T intervals and subjects is illustrated in Fig. 7A. The conditioned reflex was significantly depressed as the hip was flexed, reaching an overall size of 79.19 ± 9.9% of $Ho^{homonymous}$. The reflex depression did not differ significantly across the C-T intervals tested ($P > 0.05$). In contrast, when the hip was extended, the conditioned H-reflexes were not significantly different from control reflex values ($P > 0.05$) at any of the C-T intervals tested.

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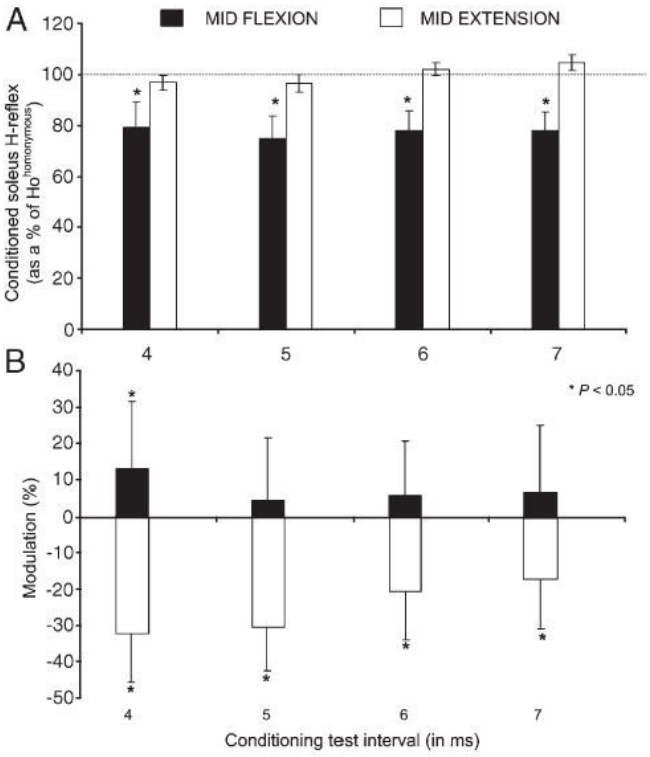

Fig. 7 Effects of synergistic muscle afferent excitation medial gastrocnemius (MG) on the soleus H-reflex during sinusoidal hip movements. (A) Pool data (all subjects tested) showing the effects of MG nerve stimulation on the soleus H-reflex for all C-T intervals tested during imposed hip movement. (B) Modulation of autogenic group I inhibition during imposed sinusoidal hip flexion and extension. A decrease in modulation is presented with negative values whereas an increase is shown with positive values. In all cases, the modulation was estimated based on Eq. (1). Error bars designate the SEM and asterisks indicate cases with statistically significant differences ($P < 0.05$) in both graphs.

The modulation of autogenic group I inhibition that the MG exerted over the soleus motoneurons, estimated using Eq. (1) (see 'Exp. Procedures') depended on the direction of the hip movement (Fig. 7B). The autogenic inhibition was markedly decreased during hip extension and increased during hip flexion. This is in agreement with the modulation of reciprocal Ia inhibition (compare Fig. 3B with Fig. 7B).

Fig. 8 illustrates the normalized activity of all muscles recorded in each subject (grey lines) as well as the average of all subjects (black lines) when the soleus H-reflex was conditioned with MG stimulation at 6 ms as the hip moved in extension (Fig. 8A) and flexion (Fig. 8B). Again, the SOL and MH displayed the most constant responses, being present during hip extension and flexion, respectively. The MG showed some activity that coincided with the

timing of the stimulus during hip flexion or extension. Further, although TA, VM, and VL responses coincided with the timing of the stimulus, bursts of activity were also present in the TA and VM during hip flexion (stimulus was sent during hip extension) and in the VL during hip extension (stimulus was sent during hip flexion).

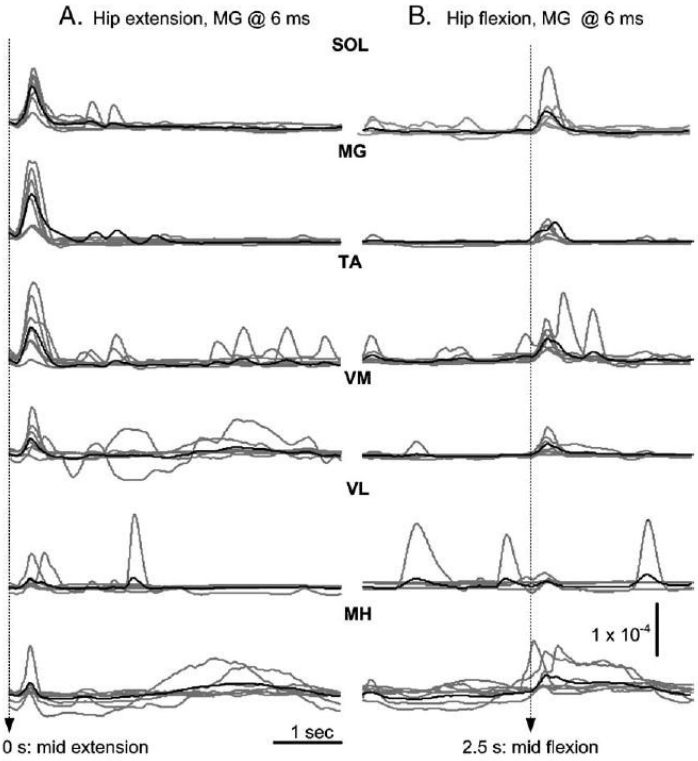

Fig. 8 Normalized average EMGs during sinusoidal hip extension (A) and flexion (B) when the soleus H-reflex was conditioned by medial gastrocnemius (MG) nerve stimulation at the conditioning test intervals of 6 ms. The grey lines indicate muscle responses (average of 10 consecutive hip movement cycles) from individual subjects, and the black lines indicate the average of all seven subjects. The vertical dotted lines identify the position of the hip (0 s for mid-extension, 2.5 s for mid-flexion) during which the soleus H-reflex was conditioned by MG nerve stimulation. SOL, TA, VM, and MH muscle responses occurred regardless the timing of the stimulus. For example, MH was active during hip flexion whereas the stimulus was delivered with hip in extension.

The reflexive torques produced by the hip, knee, and ankle joints during imposed sinusoidal leg movement when both the posterior tibial and MG nerves were stimulated at a C-T interval of 6 ms are illustrated in Fig. 9. The torques at the hip were mostly extensor, regardless of the stimulus timing in respect to the phase of the hip movement, with only brief periods of hip flexion. An extensor torque at the hip coincided with a knee flexion torque when the hip was in flexion and with a knee extensor torque when the hip was in extension. The torques of the ankle joint were generally in dorsiflexion

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when the hip was moving from mid to peak flexion, whereas the ankle torques were in plantar flexion when the hip was moving from mid to peak extension. It is clear that the hip torques were opposite to the knee torques only when the hip was in flexion and coincided with an ankle dorsiflexion torque. A similar pattern of joint torque responses was also observed at the remaining C-T intervals tested, but also when the soleus H-reflex was elicited without any conditioning stimulation.

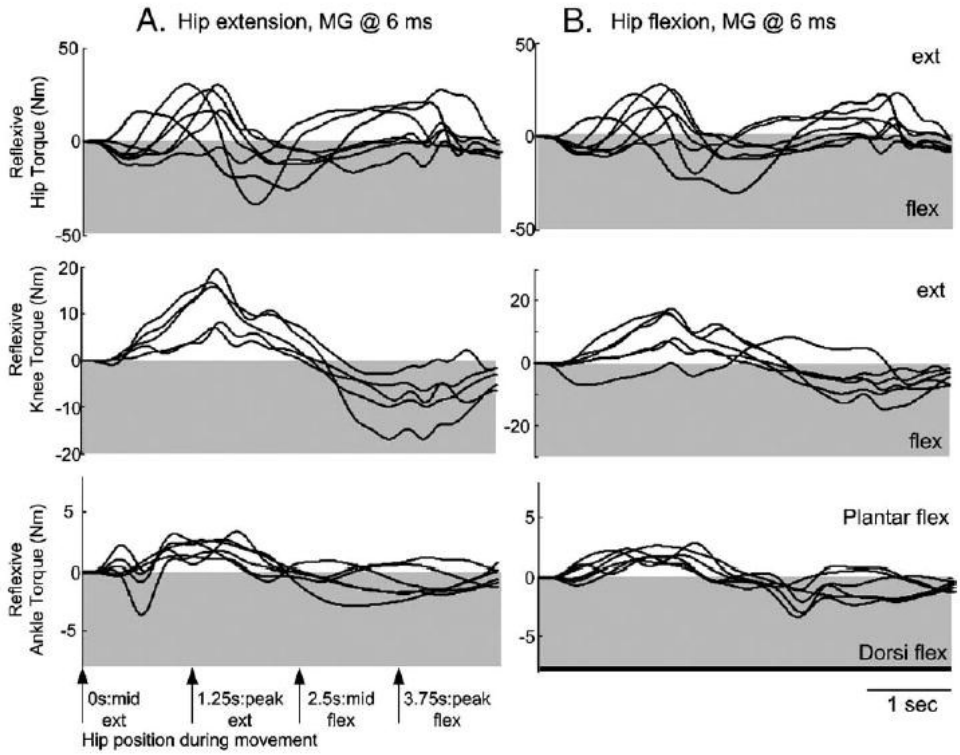

Fig. 9 Hip, knee, and ankle reflexive torques (Nm) when the soleus H-reflex was conditioned by medial gastrocnemius (MG) nerve stimulation at 6 ms during hip extension (A) and hip flexion (B). Each waveform represents the average of 10 recordings from each subject. Arrows indicate the position of the hip during the sinusoidal movement (mid-extension at 0 s, peak extension at 1.25 s, mid-flexion at 2.5 s, and peak flexion at 3.75 s). Torques above zero designate extension and those below zero designate flexion. Note the extensor torques at the hip regardless the timing of the stimulus, and that hip and knee torques occurred in opposite directions.

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3. Discussion

3.1. Modulation of spinal inhibitory mechanisms during hip movement

Modulation of reciprocal Ia and pre-synaptic inhibition was found to depend on the phase of the hip movement. In particular, the inhibition acting both pre- and post-synaptically was decreased during hip extension. In contrast, potentiation of inhibition was observed during hip flexion. These findings suggest that reflex facilitation during hip extension and reflex depression during hip flexion (Knikou and Rymer, 2002b; Chaudhuri et al., 2006) might be related to depression of the Ia and pre-synaptic inhibitory interneurons or to reinforcement of actions of inhibitory pathways, respectively. Nonetheless, recruitment of group I excitatory pathways between the hip and soleus muscle afferents is also feasible.

Our findings strongly agree with the reinforcement of the reciprocal inhibition during the swing phase of walking (Pratt and Jordan, 1987; Lavoie et al., 1997; Petersen et al., 1999) and the rhythmic changes in pre-synaptic inhibition of soleus Ia afferent terminals during walking (Capaday and Stein, 1986; Faist et al., 1996). The loss of inhibition during hip extension could contribute to clonus of the ankle during the stance phase of gait, impairing control of locomotion. However, we should note that our study was conducted with subjects supine and hip proprioceptors might modulate these inhibitory circuits differently during assisted walking in SCI patients. In this respect, the sinusoidal hip motion employed in this study was clearly slower than the movements anticipated to occur during human walking, and differences in body positions (supine vs. upright) constitute an additional factor that needs to be considered. Thus, the current data should be interpreted cautiously with respect to studies performed in humans during walking because the two conditions differ significantly.

The underlying SOL muscle responses were mostly observed as the hip passed mid-extension, whereas MH muscle responses were present during hip flexion (Fig. 4). MH activity coincided with knee flexion torques, which is in line with its expected function at the knee. Torques at the hip were mostly positive (producing an extensor moment) regardless of the timing of the stimulus and coincided mostly with knee flexion torques. It is apparent that muscle and joint torque responses were entrained to the hip movement when the reciprocal pathway was excited, similar to a previous study (Steldt and Schmit,

2004). However, we observed differences in the reflexive hip flexion and knee extension torque compared to the previous study, which might be related to the lower frequency of hip oscillation used in the current study. We propose that the underlying muscle activity in the SOL and MH could be the result of activation of a complex spinal circuit that might be linked to the modulation of inhibitory pathways described in the current study.

Excitatory and inhibitory inputs from proprioceptive afferents onto Ia and pre-synaptic inhibitory interneurons have been postulated in man, with the magnitude of the inhibition known to depend on the direction of the movement. For example, pre-synaptic inhibition of Ia afferents not involved in the movement increases as the movement begins (Hultborn et al., 1987), whereas a tonic level of pre-synaptic inhibition of Ia afferents exists when subjects are at rest (Hultborn et al., 1987). Pre-synaptic inhibition is known to control the amplitude of the monosynaptic reflexes independent of the recruitment level of the motoneuronal pool (Capaday and Stein, 1989) and can switch the activity of interneurons that are under segmental and supraspinal influences (McCrea, 1992). Thus, the contribution of pre-synaptic inhibition to movement is crucial. Interneurons mediating pre-synaptic inhibition likely project to the synapses of the Ia afferents with the Ia inhibitory interneurons (Enriquez-Denton et al., 2000), which suggests that reciprocal inhibition is affected by pre-synaptic mechanisms. This further supports the similar modulation pattern of reciprocal and pre-synaptic inhibition that we observed during sinusoidal hip movement.

The autogenic inhibition exerted from the MG onto soleus motoneurons was modulated similar to that of reciprocal Ia and pre-synaptic inhibition; being decreased during hip extension and increased during hip flexion (Fig. 7). A short-latency soleus H-reflex depression is observed following MG nerve stimulation at group I strength in spinal intact subjects at rest (Pierrot-Deseilligny et al., 1979). This autogenic inhibition has been attributed to group Ib muscle afferents based largely on studies in non-human primates (Hongo et al., 1984). It is well established that this spinal pathway is reorganized during walking. Activation of group Ib afferents during locomotion enhances extensor activity in spinal and decerebrate cats (Conway et al., 1987; Gossard et al., 1994) and in humans during the stance phase of walking (Stephens and Yang, 1996; Pearson and Collins, 1993). We found that autogenic inhibition during sinusoidal hip movements is modulated in a manner similar to that observed during walking.

Upon excitation of synergistic group I afferents, muscle responses were generally depressed compared to what was seen following excitation of the antagonistic muscle afferents, suggesting that motor output changes upon excitation of different types of afferents during hip movement. The most prevalent muscle response was that of the MH, which was present again as the hip passed mid-flexion (Fig. 8). The reflexive joint torques were similar to those previously observed, but they were expressed in a more stereotyped pattern. Specifically, hip extension torques coincided with knee and ankle flexion torques (Fig. 9). The hip, knee, and ankle joint torques occurred in the same direction as occurs in human walking, particularly at heel-off when the stance-to-swing transition occurs (Smith et al., 1996). Further, they appeared in the same direction as those recorded when spasms were initiated by the imposed hip movements (compare Fig. 5D with Fig. 9).

This spastic motor behavior is very common after chronic SCI (especially in motor incomplete) and can be initiated by a range of stimuli such as changes in body posture or excitation of thermoreceptors and cutaneous afferents. Nonetheless, the mechanisms associated with the development of spasms are poorly understood. It is likely that faster hip movements might have induced spasms in all SCI patients; however, oscillatory involuntary muscle activity was observed in 4 out of 7 subjects when H-reflexes were conditioned by CPN stimulation at long C-T intervals during hip flexion and extension but also during sinusoidal hip movement without any peripheral nerve stimulation.

The clonus-like activity that occurred during the transition of the hip from flexion to extension (see Fig. 6) might be mediated by the reflexive muscle contractions (Figs. 4 and and5),5), but also it may involve a central oscillator (Beres-Jones et al., 2003; Wallace et al., 2005). Based on our findings, it is apparent that excitation of hip proprioceptors contributes to the manifestation of extensor spasms in people with SCI, in line to similar reports (Schmit and Benz, 2002). A state transition in segmental reflex pathways has been reported in man during walking (Faist et al., 2006), and based on our findings it may partly account for the manifestation of spasms in human SCI. Given the similar pattern of reflexive joint torques during excitation of MG Ib afferents and imposed hip movement induced spasms, it is suggested that spasms and the reflex circuits in which ankle extensor afferents (Ib) are involved may share common interneuronal pathways.

3.2. Significance of hip proprioceptors to motor recovery of SCI

Ia transmission to α-motoneurons (Mailis and Ashby, 1990), reciprocal Ia, and autogenic inhibition (Boorman et al., 1996; Crone et al., 2003) as well as pre-synaptic inhibition (Morita et al., 2001) are all likely to be impaired in spastic disorders and to contribute to the complex syndrome called spasticity. Modulation of these inhibitory control systems is not evident during static hip angle changes in human SCI (Knikou, 2005), supporting the notion that hip proprioceptors modulate these inhibitory circuits when ongoing signals for hip position and muscle stretch are present, as occurs during walking. Given that cyclic modulation of inhibitory interneurons has been associated with the modulation of reflex transmission during walking in spinal intact subjects (Capaday and Stein, 1986; Faist et al., 1996), it is proposed that interaction of hip proprioceptors with spinal inhibitory control systems may at least partly account for the locomotor recovery that has been reported in these patients (Dietz et al., 1998, 2002).

Sensory feedback associated with hip position and loading is known to contribute to the regulation of gait. Research studies conducted mainly in lower vertebrates have provided evidence that these signals arise from Golgi tendon organs in ankle extensors (Conway et al., 1987) and from muscle spindles in the hip flexors (Hiebert et al., 1996; Kriellaars et al., 1994). The contribution of hip proprioception to walking has been established in infants (Pang and Yang, 2000, 2001) and in people with SCI during assisted walking (Dietz et al., 1998, 2002; Dobkin et al., 1995). After SCI, sensory signals from the hip affect the walking pattern by enhancing the swing phase (Dietz et al., 1998, 2002), whereas they interact with signals transmitting load, a signal that is fully integrated by the isolated spinal cord (Harkema et al., 1997).

Together with the evidence from the current study, these observations suggest that hip proprioceptors might contribute to locomotion recovery by adjusting pre- and post-α-moto-neuronal excitability via their access to inhibitory neuronal circuits. However, the present study was conducted with subjects supine, so further research is needed to investigate the interaction between the hip proprioceptors and spinal inhibitory control systems during assisted walking after SCI in humans thus to determine the pathways that are involved during locomotion training and to develop training paradigms in which specific afferent groups can be triggered in a timely manner through specific sensorimotor conditioning orthosis systems.

3.3. Possible effects from inter-subject variability

The modulation of pre- and post-synaptic inhibition acting on soleus Ia afferent terminals and α motoneurons, respectively, was consistent during hip flexion and extension across subjects. Based on this observation, no conclusion could be drawn about differential effects due to the level, nature, or clinical symptoms of the spinal lesion. The lesions were classified as ASIA C in all subjects with their level ranging from C5 to T11. Similarly, 3 out of 7 subjects were taking antispastic medication at the time of the study. However, across conditioning stimulations we found no significant differences in the magnitude of the conditioned H-reflex when comparing data from subjects on spasticity medications to those under no medication ($P > 0.05$). Nonetheless, the sample size for this comparison was small, and the subjects taking antispastic medications were likely to have higher levels of spasticity before taking medication, which could have masked the effects of the drugs.

3.4. Conclusion

The present study provides evidence that actions of spinal inhibitory interneurons that act at a pre- and/or post-synaptic level are modulated by hip movement in a phase-dependent manner. The reciprocal Ia, pre-synaptic, and autogenic inhibition were increased during hip flexion and decreased during hip extension. Further, the hip, knee, and ankle joint torques were found to be similar to those observed during extensor spasms and human walking, whereas the muscle responses depended on the direction of the hip movement. Hip-mediated sensory feedback is known to shape the walking pattern after SCI and to account for phase transitions and swing phase initiation in spinal cats during fictive locomotion. Signals from the hip proprioceptors integrated at an interneu-ronal level adjust the level of inhibition acting on Ia afferent terminals or on α-motoneurons, whereas in supine SCI patients hip afferents contribute to initiation and substantiation of spasms. Analogously, hip-mediated sensory feedback might contribute to the recovery of walking after a SCI in humans by normalizing muscle tone through spinal inhibitory control circuits. Further research is needed to study the interaction of spinal interneuronal circuits with hip proprio-ceptive cues during assisted walking in people with a motor incomplete SCI so that locomotor training strategies after SCI can be improved.

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4. Experimental procedures

4.1. Subjects

All experiments were conducted following approval of the research protocol by the Office for the Protection of Human Subjects of the Northwestern University (Chicago IL, USA) and were conducted according to the 1964 Declaration of Helsinki and Belmont Report. Signed informed consent was obtained from each participant before testing. Seven subjects with chronic sensory motor incomplete SCI [American Spinal Cord Injury Association (ASIA) classification C] ranging from cervical 5 to thoracic 11 spinal segments participated in this study (Table 1). These same participants also volunteered in previous studies (Knikou, 2005, 2006a; Knikou et al., 2006) and were identified with the same numbers. At the time of the study, three of the seven subjects reported taking antispastic medications.

Subjects	Gender	Age (years)	Post-injury (months)	Ashworth score	ASIA scale	Lesion level	Sensation	Medication/day	ROM	
									CPN	MG
S1	M	24	90	1	C	C5	Intact	–	30°	30°
S3	M	28	38	0	C	C5	Intact	–	42°	54°
S4	M	46	66	2	C	C6	Intact	Baclofen 60 mg	48°	55°
S5	M	21	33	2	C	T11	Intact	Baclofen 20 mg	65°	65°
S7	F	60	38	0	C	T9	Intact	–	55°	55°
S10	M	51	198	1	C	C5	No sensation of cold/warm	Baclofen 30 mg	65°	50°
S11	M	51	174	3	C	C5	No sensation of cold/warm	–	64°	53°

Table 1 SCI subjects' characteristics[a]

[a]Spasticity at the ankle was scaled according to the Ashworth scale (Ashworth, 1964). Lesion completeness was classified according to the ASIA impairment scale (Maynard et al., 1997) with ASIA C representing a sensory and motor incomplete lesion where more than half of muscles below the injury level have a strength of less than 3 (out of 5). F, female; M, male; ROM, total range of imposed hip sinusoidal movement for tests examining the effects of antagonistic (CPN) and synergistic (MG) group I afferents excitation on the soleus H-reflex.

In all subjects, each test was conducted on different days. In test 1, we examined the effects of imposed hip movement on

reciprocal and pre-synaptic inhibition by conditioning the soleus H-reflex with a stimulus to the CPN that proceeded at variable time delays. This test was conducted twice (on separate days) to ensure repeatability of our results. In the first trial, the modulation of reciprocal and pre-synaptic inhibition during hip movements was examined when the CPN was stimulated at 3 and 100 ms C-T intervals. The modulation observed in the 1st trial and in the 2nd trial was identical (data from the first trial are not shown graphically). In test 2, we examined the effects of sinusoidal hip movements on autogenic inhibition by conditioning the soleus H-reflex with MG nerve stimulation, preceded again at variable time delays. The range of hip movement (ROM) during both experimental trials is indicated in Table 1. Different hip ROMs are reported for 4 patients. This was based largely on day-today and subject-to-subject differences in the expression of muscle tone and spasms. Specifically, the range was limited in some subjects due to associated increased hip adductor tone, which restricted the comfortable range of motion.

4.2. Experimental apparatus

With subjects supine, the right leg was secured to a leg brace with built-in single-axis torque transducers (Himmelstein Inc., Hoffman Estates, IL, USA) that were aligned with the axes of rotation for the knee and ankle joints. The hip torque was measured directly from a Biodex system (Biodex Medical Systems Inc., Shirley, NY). The leg brace was affixed to the motor head of the Biodex system. The brace's footplate had a clamp to hold the forefoot and a strap to secure the heel. The hip–knee and knee–ankle links were adjustable to accommodate each subject's leg length. The pelvis was secured with a strap across the lower trunk.

Surface electromyograms (EMGs) were recorded from the right soleus (SOL), tibialis anterior (TA), medialis gastrocne-mius (MG), medial hamstrings (MH), vastus medialis (VM), and vastus lateralis (VL) muscles in all subjects through differential bipolar electrodes (DE-2.1; DelSys, MA, USA). All electrodes were secured via self-adhesive tape and were placed following light mechanical abrasion of the skin. EMG signals were bandpass filtered (20–250 Hz) before being sampled at 2 kHz using a data acquisition card (National Instruments, Austin TX) and customized acquisition programs (LabVIEW software, National Instruments) and were archived for further analysis.

After the right leg was secured to the brace, the hip joint's center of rotation was aligned with the center of the Biodex motor head unit. Sinusoidal passive hip movements in the sagittal plane were

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imposed (and controlled) by the Biodex system using the Researcher's Toolkit pattern files (Biodex). During the sinusoidal oscillations, the hip was moved through 10 full cycles of flexion and extension at 0.2 Hz. Each hip movement cycle lasted 5 s. The ankle and knee joints were set at 20° of plantar flexion and 30° of flexion across subjects, respectively, and were held isometric by the leg brace during the sinusoidal hip movements.

4.3. Soleus H-reflex (elicitation and recording protocol)

The soleus H-reflex was elicited by stimulating the right posterior tibial nerve (PTN) in the popliteal fossa through a monopolar electrode using a 1-ms rectangular pulse generated by a constant current stimulator (DS7A; Digitimer Ltd., UK). The indifferent electrode, a circular stainless steel of 3-cm diameter disk, was placed just above the right patella for selective stimulation of the nerve trunk.

At the start of each test (subject supine) a hand-held monopolar electrode with stainless-steel head was used as a probe to establish the correct site for stimulating the PTN. This was defined as the site where the soleus H-reflex was present without the M-wave being present. After this site was identified, the probe electrode was replaced by a permanent electrode (N-10-A, Ambu Inc., Denmark) under constant pressure, and the evoked responses were observed on a digital oscilloscope (Tektronics Inc., Beaverton, OR). The procedure was repeated in case the surface electrode did not evoke the same response behavior (M-wave and H-reflex amplitude relative to stimulus intensity strength) as obtained with the probe. After the site was established, the maximal M-wave (elicited every 5 s) was measured online as peak-to-peak amplitude of the unrectified waveform using the oscilloscope and was saved for further analysis. Then, the stimulus strength was adjusted to give an H-reflex of 15–35% of the maximal M-wave on the ascending part of the recruitment curve. Subsequently, the leg frame was secured to the right leg as previously described, and 20 soleus H-reflexes elicited every 5 s were evoked again to ensure that the reflex recruitment pattern did not change. In Fig. 10A, the average size of the soleus H-reflexes recorded with subjects supine as a percentage of the maximal M-wave for both conditioning protocols is indicated. These reflexes ranged from 15% to 35% of the maximal M-wave across subjects.

The sensitivity of the H-reflex to facilitation or inhibition depends on the size of the test reflex (Crone et al., 1990). Thus, we adjusted the stimulus strength to evoke $Ho^{homonymous}$ reflexes (H-reflexes elicited when the hip was in mid-flexion without any

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sensorimotor conditioning stimulus and used to normalize conditioned reflexes recorded during hip flexion) that ranged from 15% to 35% of the maximal M-wave across subjects and verified that they were elicited on the ascending part of the recruitment curve. This was also done for hip extension trials. In Figs. 10B and C, the $Ho^{homonymous}$ reflexes recorded in each subject as a percentage of the mean size of the soleus H-reflex (subject supine, no conditioning stimulus) for both experimental trials (CPN and MG tests) during hip flexion and extension are indicated. Note that the $Ho^{homonymous}$ reflexes in flexion were not similar to those with hip in extension in only 4 out of 28 cases.

Lastly, the M-wave size was used as a screening factor for accepting conditioned H-reflexes (by CPN or MG nerve stimulation) at different C-T intervals during imposed hip movements. In case a significant difference between the M-wave of the conditioned and the $Ho^{homonymous}$ reflexes was found, the experimental data were rejected and the test was repeated on a different day.

4.4. Conditioning electrical stimuli

4.4.1. Excitation of antagonistic group I afferents (CPN)

The methods for CPN stimulation used in the present study were similar to those previously employed in the same SCI subjects (Knikou, 2005) and in other human studies (Morita et al., 1998; Meunier and Pierrot-Deseilligny, 1998). The stimulus to the CPN was a single shock of 1-ms in duration, generated by a constant current stimulator (DS7A, Digitimer Ltd., UK), and delivered with a bipolar electrode placed distal to the head of the fibula. The conditioning stimulus was delivered at motor threshold (MT) level of the TA muscle and was kept at this level throughout the experiment. Selective TA activation was ensured when activity in the peroneal muscles was not present and increases in stimulus intensity evoked ankle dorsiflexion without eversion. Further, it was essential that in all tests the MT in the TA muscle was always lower than the one in the peroneal muscles. The MT in the TA muscle was determined by the appearance of TA EMG. Constancy of conditioning stimulation was ensured by the presence of a stable, small in amplitude TA M-wave, which was monitored during the experiment using the oscilloscope (see Fig. 1B).

The ipsilateral CPN stimulation always preceded the soleus H-reflex at C-T intervals of short (2, 3, and 4 ms) and long (80, 100, and 120 ms) duration. These C-T intervals were selected because reciprocal Ia inhibition has a short latency between activation of the

agonist and inhibition of the antagonist in spinal intact subjects (Crone et al., 1987; Crone and Nielsen, 1989), whereas the reflex inhibition produced at the long C-T intervals is predominantly pre-synaptic (Iles, 1996). Conditioned reflexes using CPN stimulation at either short or long C-T intervals during hip flexion or extension were recorded randomly.

4.4.2. Excitation of synergistic group I afferents (MG)

The methods for MG nerve stimulation were similar to those first described by Pierrot-Deseilligny et al. (1979) and previously employed in the same SCI subjects (Knikou, 2005). The stimulus to the MG nerve was a single shock of 1-ms generated by a constant current stimulator (model DS7A, Digitimer, UK) and delivered with a bipolar electrode placed in a location producing a clear contraction of the MG muscle. The stimulating electrode was placed at the lower and internal part of the popliteal fossa 6–10 cm below the cathode electrode to the PTN. The stimulus strength to the MG nerve was expressed in multiples of MT in the MG muscle and was equivalent to one times MT. The surface electrodes (DelSys, USA) that recorded MG muscle activity were placed over the muscle site that showed a contraction with minimal stimulus intensity. The effects of MG nerve stimulation on the homonymous muscle were observed online with a digital oscilloscope and were checked several times throughout the experiment to ensure that MG nerve stimulation evoked a minimal M-wave in the MG muscle. Ipsilateral MG nerve stimulation always preceded the PTN stimulation (H-reflex) using conditioning-test (C-T) intervals of varying delays (i.e., 4, 5, 6, and 7 ms).

4.5. Experimental protocol

With subjects supine and the leg supported by the brace, the correct sites for soleus H-reflex elicitation and CPN/MG nerves stimulation were established as previously described. The total range of movement at the hip was then determined (Table 1) and used to generate pattern files (Biodex) that moved the leg through this range for the rest of the experiment. As the leg moved passively from flexion to extension, a custom LabVIEW program collected the torque, EMG, and position data. Depending on the trial requirement (whether the stimulus was sent during hip flexion or extension), the LabVIEW program also triggered the constant current stimulators (Digi-timer, Hertfordshire, UK) that were timed with the imposed flexion and extension movements at the hip. Depending on the test condition, the stimulus was sent once at mid-cycle, either at 0 s for extension trials or at 2.5 s for flexion trials of a hip movement cycle (start point hip

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flexion, leg moved in extension and return to the start point) that lasted 5 s.

The $Ho^{homonymous}$ reflexes were recorded during imposed sinusoidal hip movements as described previously. Then, conditioned reflexes (H-reflex preceded by CPN stimulation at short and long C-T intervals while the hip was in flexion) were recorded again. The $Ho^{homonymous}$ was recorded at least twice and was recorded in random order with the conditioned reflexes. The M-wave magnitude was continually monitored to ensure stability in the stimulation and recording procedures and constituted the intra-subject criterion for accepting the conditioned H-reflexes during hip movement. Thus, the stimulus was adjusted in order to maintain a constant M-wave across the experimental conditions. For example, when the M-wave of the conditioned H-reflex was different from the M-wave of the control reflex (both reflexes recorded during hip movement), the stimulus intensity was adjusted so that the sizes of the M-waves of both reflexes were similar. The same experimental protocol was followed for reflex recordings collected with the hip in mid-extension and for MG nerve stimulation during sinusoidal hip flexion and extension.

In each experimental session, surface EMG and joint torques were collected during imposed hip movements (10 cycles) when none of the mixed peripheral nerves were stimulated. The data from the hip movement cycle with no detectable activity in the muscles were used as a measurement of the combined effects of inertia, gravity, and passive resistance of the limb and instrumented leg brace.

4.6. Off-line data analysis

The pattern of muscle responses produced by the sinusoidal oscillation at the hip was characterized for each subject in order to establish the effects of hip movement on the timing and duration of the muscles responses when spinal inhibitory control systems were examined. For each subject and trial, the EMG data for each muscle were band-pass filtered (20–500 Hz, all filters were Butterworth 2nd order filters with no phase lag), full-wave rectified, smoothed, and averaged over the 10 consecutive hip movement cycles. Then, the average EMG signal for each muscle was normalized by its average integrated area under the rectified curve, and the resultant normalized EMG was plotted as a function of time.

The joint torque data produced by the imposed sinusoidal hip oscillations during which no peripheral nerves were stimulated and muscles were quiescent were used to determine the underlying

reflexive effects produced at the hip, knee, and ankle in the trials of sensorimotor conditioning of the soleus H-reflex. A movement cycle without any detectable muscle activity was used to estimate the effects of passive movement, inertia, and gravity on joint torques of the leg and brace. In order to do this, for each subject, the hip, knee, and ankle joint torques from the hip movement cycle during which muscles were quiescent were aligned with the respective joint torques produced when conditioned soleus H-reflexes were recorded. The difference between them was calculated as the reflexive torque response initiated by the hip movement. These signals were low-pass filtered at 2 Hz, and the average of the filtered data from 10 hip movement cycles was identified as the torque response for each specific joint and subject.

4.7. Statistical data analysis

The soleus H-reflex and M-wave of the control ($Ho^{homonymous}$) and conditioned reflexes were full-wave rectified and their sizes were measured as the area under the corresponding waveform. The reflexes recorded at each C-T interval as the hip flexed or extended were expressed as a percentage of the mean size of the control reflex collected with the hip in the same orientation of flexion or extension ($Ho^{homonymous}$). Analysis of variance (ANOVA) for repeated measures was applied to the experimental data sets for each subject in order to determine statistically significant differences between the control and the conditioned H-reflexes during hip flexion and extension. The mean size of each subject's conditioned reflex was then grouped based on the C-T interval and hip movement investigated. A two-way ANOVA with repeated measures was applied to the data to establish changes in the size of the conditioned reflexes across C-T intervals and hip movements.

For each subject, the sizes of the M-waves of the $Ho^{homonymous}$ and conditioned H-reflexes were expressed as a percentage of the maximal M-wave. ANOVA for repeated measures was used to test for differences between the M-waves of the reflexes recorded under control conditions and following sensorimotor conditioning during hip flexion and extension. When significant differences were encountered, the trial was rejected.

Hip proprioceptive cues are a strong modulator factor of spinal reflex excitability in people with motor complete or incomplete SCI (Knikou and Rymer, 2002b; Chaudhuri et al., 2006). Thus, a mathematical estimation (Eq. (1)) of the modulation of reciprocal, pre-synaptic, and autogenic inhibition during imposed hip movements was

conducted. This was done so to establish the net modulation of these spinal inhibitory systems having extracted the effects that hip movement might have had induced on spinal reflex excitability or on inhibitory/facilitatory neuronal pathways.

$$\text{Modulation}=(\text{Hcond}/\text{Ho}^{\text{Homonymous}})-(\text{Ho}^{\text{Homonymous}}/\textit{Ho})\%. \quad (1)$$

In this equation, $\text{Hcond}/\text{Ho}^{\text{homonymous}}$ (%) represents the H-reflex recorded during sinusoidal hip flexion or extension conditioned by CPN (or MG) stimulation at short or long C-T intervals expressed as a percentage of the mean size of the associated control reflex ($\text{Ho}^{\text{homonymous}}$). $\text{Ho}^{\text{homonymous}}/\text{Ho}$ (%) represents the soleus H-reflex recorded during dynamic hip flexion or extension without a CPN (or MG) stimulus expressed as a percentage of the reflex recorded with subjects supine. A negative value indicates a condition associated with decrease in inhibition, whereas a positive value indicates a condition that is associated with potentiation of the inhibitory effects. Statistically significant differences were established at 95% of confidence level. Results are presented as mean values along with the standard error of the mean (SEM).

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Footnotes

[1]$\text{Ho}^{\text{homonymous}}$ represents the control H-reflex recorded during hip flexion (without any electrical conditioning stimulus being present) and is used to normalize the reflexes conditioned by CPN stimulation at short and long C-T intervals during hip flexion. The same applies for reflexes recorded during hip extension.

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