Rhythmic Arm Cycling Induces Short-term Plasticity of Soleus H-reflex Amplitude

by

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B.Sc. in Physiotherapy, University of Medical Sciences, Iran, 1998

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ABSTRACT

Plasticity in spinal networks has been proposed as a means to permit motor skill learning and recovery after central nervous system disorders. This plasticity is significantly driven by input from the periphery (Wolpaw & Carp, 2006). For instance, attenuation of soleus Hoffmann (H) reflex can last beyond the period of different types of conditioning via putative presynaptic inhibition (Brooke et al., 1997). Interestingly, rhythmic arm cycling can also attenuate soleus H-reflex via interlimb connections and presynaptic pathways (Frigon, Collins, & Zehr, 2004). However, it remains to be studied if this attenuation is maintained beyond the period of arm cycling. In this study, we hypothesized that excitability of H-reflex pathway would remain suppressed after cessation of arm cycling. Subjects were seated with their trunk and feet fixed at a neutral position. Using an arm ergometer, they cycled at 1Hz for 30min. H-reflexes were evoked via stimulation of the tibial nerve in the popliteal fossa at 5 minute intervals. These intervals began prior to the cycling and continued during cycling and up to 30 minutes

after termination of cycling (n=12). Besides soleus muscle, electromyography was recorded from tibialis anterior, vastus lateralis and biceps femoris. Stimulation was set to evoke an M-wave which evoked an H-reflex on the ascending limb of the recruitment curve (size was 75% H_{max}) obtained prior to cycling. The M-wave amplitude was maintained throughout all trials by monitoring and adjusting the level of stimulation intensity. All H-reflex and M-wave data were normalized to the averaged M_{max} to reduce inter –subject variability. The main result was that the suppression of H-reflex amplitude persisted beyond the period of arm cycling. H-reflex amplitudes were significantly ($p<0.05$) smaller up to 20 min after arm cycling had stopped. This suggests that arm cycling can induce plastic adaptation in the soleus H-reflex pathway that persists well beyond the period of conditioning. Also, in an additional experiment (n=8), the prolonged effect of arm cycling combined with superficial radial (SR) nerve stimulation was investigated. Interestingly, this cutaneous nerve stimulation cancelled out the prolonged suppression of H-reflex amplitude induced by arm cycling. Since SR nerve stimulation facilitates soleus H-reflex via reductions in the level of Ia presynaptic inhibition (Zehr, Hoogenboom, Frigon, & Collins, 2004), persistence in presynaptic inhibitory pathways is suggested as an underlying neural mechanism. These results have relevance for optimizing rehabilitation techniques in the treatment of spasticity which is known to be related to the H-reflex size (Levin & Hui-Chan, 1993).

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DEDICATION

This work is dedicated to my grandma for her endless love, my parents for the support they have provided throughout my entire life, my siblings, Morteza and Mojgan, and my nieces and nephew, Nazanin, Kiana, Helia, and Iman who have added so much to the beauty of our world.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

There has been an increasing interest in the concept of activity-dependent plasticity of neural function as it provides the basic understanding of the extent that the central nervous system (CNS) can express short or long term adaptations. These adaptations occur in response to different interventions, such as specialized exercise or training. This is considered as essential knowledge for designing improved rehabilitative and training paradigms.

It has been shown that spinal reflexes are amenable to plastic adaptation as observed as changes in their excitability (Wolpaw & Tennisen, 2001; Aagaard, 2003; Wolpaw & Carp, 2006; Zehr, 2006). Rhythmic movements can induce short and long term adaptation in excitability of these reflexes, which make them useful tools for studying the concept of activity-dependent plasticity. Here, the main focus is to review literature relating to the hypothesis that a remote rhythmic movement can induce long lasting changes in the excitability of spinal circuits. First, the role of central pattern generators and interlimb linkages in induction of rhythmic movement are discussed. Then, the concept of spinal plasticity and putative sources of plasticity are explained. Finally, the acute and chronic effects of movement on spinal reflexes are clarified and extended to interlimb coupling and particularly, the effect of remote movement on soleus H-reflex modulation.

Central pattern generators (CPGs)

Locomotion, whether walking, swimming, or flying, is largely produced by interconnected spinal neurons that make up central pattern generators (CPGs) (Grillner &

Wallen, 1985; Rossignol et al., 1996; Orlovsky, Deliagina, & Grillner, 1999; Dietz, 2003; Zehr, 2005). These networks generate rhythmic movement and consist of those interneurons (IN) involved in timing and oscillatory behavior and those that are related to mediating somatosensory feedback and reflex pathways (reviewed in (Zehr, 2005; Dietz, 2003). The idea of CPGs originated from Brown's work in the early twentieth century. He showed that, after deafferentation of spinalized cats, the spinal cord was still capable of inducing reciprocal activity in flexor and extensor muscles (Brown, 1911; Brown, 1914).This "fictive locomotion" is considered direct evidence for the existence of CPGs in an isolated spinal cord (Dietz, 2003).

In humans with long-lasting complete spinal cord injured person (SCI) a patterned CPG- like activity can be elicited by applying epidural electrical stimulation to the L2 segments (Dimitrijevic, Gerasimenko, & Pinter, 1998). Moreover, rhythmic leg muscle activation patterns can be elicited in clinically complete SCI when stepping with assistance on a treadmill using body-weight support (Maegele, Muller, Wernig, Edgerton, & Harkema, 2002).These results suggest that, similar to cats, human spinal cords are capable of generating rhythmic activity independent of supraspinal input. However, the independence of the isolated spinal cord to generate locomotor movements is notably greater in spinalized cats than in humans (Dietz, Colombo, Jensen, & Baumgartner, 1995; Dietz, 2003). Studying infants during treadmill locomotion has provided further evidence for the existence and behavior of CPGs in humans. At an age where corticospinal connectivity is weak or absent, infants are able to respond to perturbation by using sensory feedback to modify the locomotor cycle, and make different patterns of walking such as forward, backward, and side walking (Yang et al., 2004).

Additionally, reflex studies have been used as a non-invasive technique to investigate the neural control of human locomotion. The reflexes studied most often have been cutaneous (stimulation of a cutaneous nerve yielding oligosynaptic responses) and Hoffmann (H-) reflex (electrical analogue of spinal stretch-reflex (SSR) which is characterized by monosynaptic and oligosynaptic projections of group Ia afferents onto homonymous motoneurons) (Burke, Gandevia, & McKeon, 1984). During locomotor tasks, comparable patterns of muscular contractions along with similar modulation of spinal reflexes in arms and legs has been attributed to the role of CPGs in regulating rhythmic movements in human (Zehr & Kido, 2001; Zehr, Collins, Frigon, & Hoogenboom, 2003; Zehr & Haridas, 2003; Duysens & Van de Crommert, 1998; Zehr, 2005). These authors suggest that CPGs are assisted by sensory feedback to regulate excitability of specific motoneuronal pools necessary for each task while supraspinal input likely regulates activity in the oscillating circuits to permit different behavioral needs such as walking faster or slower.

Interlimb neural coupling and reflex modulation

Reduced animal studies

Coordination of the fore and hindlimbs (i.e. interlimb coordination) has been recognized as a feature of quadrupedal locomotion which has been exclusively ascribed to CPGs. Studies of the feline spinal cord have shown that enlargements of the cervical and lumbosacral areas are connected by long propriospinal neurons (Miller, Reitsma, & Meche, 1973; Miller, Van Der Burg, & Van Der Meche, 1975). These pathways were found to connect the cervical enlargement to L2 and S2 segments of spinal cord (Skinner, Adams, & Remmel, 1980; Krutki, Grottel, & Mrowczynski, 1998). Also, triple ascending

projections from sacral segments to C6, cerebellum and reticular formation have been identified (Grottel, Krutki, & Mrowczynski, 1998). Interlimb reflexes (i.e. stimulating nerves in the hindlimb and recording from the muscles in the forelimb and vice versa) have also been used as an indirect method for studying interlimb connections. Miller et al. (1973) showed that stimulation of hind limb nerves strongly influences the excitability of the different groups of motoneurons supplying muscles of the forelimb via propriospinal pathways. Conversely, stimulation of forelimb nerves strongly influences the excitability of hind limb motoneurons (Schomburg & Behrends, 1978). More recent study in isolated spinal cords of neonatal rats has shown that lumbar CPGs mediate a powerful ascending excitability gradient to the cervical CPG (Juvin, Simmers, & Morin, 2005). Together, evidence supports the existence of interlimb connections in the spinal cord of quadrupeds which connects cervical and lumbar CPGs to induce coordinated movement during locomotion (see review (Dietz, 2003).

Human studies

Similar to quadrupeds, rhythmic activities such as walking, running, and swimming require the coordination of arms and legs in the human. In the human spinal cord, caudal to the cervical enlargement, reticulospinal fibers are progressively replaced by propriospinal fibers but some may still descend to the lowest sacral segments (Nathan, Smith, & Deacon, 1996). The presence of these propriospinal connections between the cervical and lumbosacral enlargement suggests that they might be functionally important in interlimb coordination (Skinner et al., 1980). This interlimb connection has been further studied by examination of spinal reflexes in spinal cord injured subjects. Electrical stimulation of mixed nerves in the leg of spinal cord subjects caused reflex

responses in the muscles of both arms. Therefore, it is likely that generating interlimb reflexes in spinal cord subjects is independent of supraspinal connections, suggesting that propriospinal pathways have crucial contributions in interlimb connections (Calancie, 1991; Calancie, Lutton, & Broton, 1996; Calancie, Molano, & Broton, 2002).

Further studies on interlimb coupling rely on testing spinal reflexes in normal subjects. Using the intrathecal technique, Sarica and Ertekin (1985) reported direct evidence of interlimb reflex action between the arms and legs. Following stimulation of the median nerve at the elbow, descending lumbosacral cord potentials (DLCP) were recorded which were above or around the excitation threshold of motor nerve fibers and could not be produced by pure skin nerve stimulation. The onset of DLCP is at very short latency (mean 12.1 ms). Hence, it was concluded that the potentials are conducted through fast propriospinal pathways which could be important in the coordination of movement and posture in human (Sarica & Ertekin, 1985). Also, stimulation of the sural nerve causes a biphasic facilitation of H-reflexes in the biceps and triceps brachii. The first peak of facilitation occurs at 35-45 ms latency which excludes supraspinal influences (Delwaide & Crenna, 1984). Similarly, electromyography (EMG) of various tonically activated leg muscles shows that brachial nerve stimulation exerts stereotypical reflex responses which regularly consist of an initial depression phase (60 ms) and a subsequent facilitatory phase (80 ms) (Meinck & Piesiur-Strehlow, 1981). Following cutaneous stimulation at the shoulder and upper arm, soleus H-reflexes are facilitated at 20-40 ms latency (i.e. the time between preceding cutaneous stimulus and the H-reflex stimulation) which persists until 100-150 ms (Gassel & Ott, 1973), via decreased presynaptic inhibition of the H-reflex pathway (Kagamihara, Hayashi, Masakado, & Kouno, 2003).

The fact that remote cutaneous stimulation can facilitate the soleus H-reflex pathway at such short latencies is suggestive of a direct effect of remote cutaneous input via propriospinal pathways. This was further confirmed by a recent study in which stimulation of cutaneous nerves at the wrist (superficial radial nerve) and at the ankle (superficial peroneal nerve) evoked interlimb reflexes in arm and leg muscles with latencies of less than 75 ms. This latency is shorter than the earliest possible latency for a transcortical reflex, suggesting that interlimb reflexes are conveyed via propriospinal pathways (Zehr, Collins, & Chua, 2001).

Postural modification has also been used to study the interlimb connections and possible transfer of proprioceptive and extroceptive input. When the ipsilateral upper limb is in flexion and the contralateral is in an extended position, a facilitation of ipsilateral soleus H-reflexes was observed. Also, soleus H-reflexes are inhibited when this pattern is reserved (Delwaide, Figiel, & Richelle, 1977). In a recent study, Frigon et al. (2004) showed that there was no significant difference between H-reflexes evoked at shoulder flexion and extension during static positions. Additionally, during arm cycling, no significant effect of arm position on the soleus H-reflex excitability was found (Loadman & Zehr, 2007). This suggests that remote proprioceptive input evoked by movement does not affect the H-reflex pathway directly. However, these inputs may influence CPGs by which all the somatosensory inputs are incorporated to induce coordinated movement between arms and legs (Frigon et al., 2004; Loadman et al., 2007).

Overall, the evidence supports the existence of interlimb connections in the human spinal cord which could contribute to interlimb reflex modulation and coordination during locomotion.

Adaptive plasticity of spinal cord

Plasticity means the capacity to be molded or altered. In the central nervous system, motor plasticity refers to the capability of the CNS to produce compensatory adaptations which permit motor skill learning and recovery after disorders (Wolpaw et al., 2001; Wolpaw et al., 2006). This adaptation can be short term (i.e. acute adjustment) or long lasting (i.e. chronic plasticity). For instance, muscle reflexes are modulated rapidly during locomotion in an adaptive manner within each phase of the step cycle (Stein, Yang, Belanger, & Pearson, 1993). The CNS can also adapt slowly in response to age (Sabbahi & Sedgwick, 1982; deVries, Wiswell, Romero, & Heckathorne, 1985), particular demands such as learning new skills (Nielsen, Crone, & Hultborn, 1993; Ung, Imbeault, Ethier, Brizzi, & Capaday, 2005) or due to effects of CNS disorders such as spinal cord injury (Calancie et al., 2002; Dietz & Muller, 2004; Edgerton, Tillakaratne, Bigbee, de Leon, & Roy, 2004).

Spinal reflexes have been widely used as probes to investigate adaptive plasticity in the human nervous system (Wolpaw et al., 2001; Wolpaw et al., 2006). These reflexes are shown to be amenable to plastic adaptation as direct or indirect effect of activity or training. Operant conditioning is the best example of studies in which modification of the reflex is directly targeted. However, strength training or locomotion retraining can be considered as contexts in which H-reflexes are modified indirectly (for review see (Zehr, 2006). The reflexes studied most often have been the spinal stretch-reflex (SSR)

produced largely by the Ia- motoneuron pathway, and its electrical analogue, the Hoffmann (H-) reflex. Adaptive changes in theses reflexes have been used to elucidate the role of descending input as a putative source of spinal plasticity.

Role of supraspinal input

Operant conditioning of the SSR or H-reflex has been used as a simple laboratory model to provide insight into the complex patterns of spinal and supraspinal plasticity that underlie skill acquisition in normal life. In the standard protocol of operant conditioning, SSR or H-reflex size (recorded as EMG response) is considered as the behavior. The consequence or reward occurs when this response is above (for up conditioning) or below (for down conditioning) a criterion level. The intriguing finding is that when the reward is imposed, SSR increase or decrease appears to occur in two distinct phases. Phase I has been suggested to indicate a nearly immediate change in suprasegmental influence of the segmental arc of the SSR. Phase II reflects gradual spinal cord plasticity caused by prolonged continuation of the descending influence (Wolpaw, Noonan, & O'Keefe, 1984). Interestingly, the effect of conditioning can persist even after the spinal cord is isolated from the brain (Wolpaw, Carp, & Lee, 1989). Therefore, it remains possible that plasticity of the spinal cord might simply preserve the changes which are caused due to ongoing descending activity interacting with peripheral input. However, studies of spinalized cats and SCI patients have highlighted the capability of spinal cord for adaptive changes when the supraspinal inputs are absent or reduced.

Role of somatosensory input

Treadmill training in spinal cord transected animals has provided valuable information about the importance of somatosensory feedback in spinal plasticity. It has been shown that spinal cats are capable of walking if they receive treadmill training after injury (Forssberg, Grillner, Halbertsma, & Rossignol, 1980; Barbeau & Rossignol, 1987; Rossignol, Bouyer, Barthelemy, Langlet, & Leblond, 2002; de Leon, Hodgson, Roy, & Edgerton, 1998; De Leon, Hodgson, Roy, & Edgerton, 1999). Proprioceptive signals during limb loading are largely responsible for the recovery of treadmill stepping in chronic spinalized cats (Edgerton et al., 1992). Recently, it was shown that step training modifies transmission from group I afferents of the extensor muscles in spinalized cats (Cote, Menard, & Gossard, 2003). Cutaneous (exteroceptive) feedback also plays a significant role in spinal plasticity. In an innovative study by Muir and Steeves (1995), it was shown that ground contact during stance activates cutaneous receptors which are essential for recovery of locomotion. Recently, a high degree of specificity in plasticity among cutaneous pathways was shown in spinal cats, indicating that step training could particularly modify transmission of skin inputs signaling ground contact (Cote & Gossard, 2004). This highlights the crucial role of cutaneous as well as proprioceptive feedback in plasticity of the spinal cord.

Similar to cats, in humans with incomplete SCI, treadmill training can improve over-ground walking ability. Also, increased weight bearing activates proprioceptive feedback which improves stepping ability on a moving treadmill (Barbeau et al., 1987; Edgerton et al., 1992; Barbeau, Wainberg, & Finch, 1987; Wernig, Muller, Nanassy, & Cagol, 1995). Cutaneomuscular stimulation was also shown to partially restore normal

reflex modulation in spastic SCI patients (Fung & Barbeau, 1994).Considering the results from the reduced animal studies, it seems that supraspinal feedback is still critical in functional recovery of the human spinal cord. The difference between primates and cats may be related to the increased importance of the cortico-spinal tract in primates, relying more on the supraspinal drive to maintain an upright posture and also provide free movements of upper limb from locomotor movements (Vilensky & O'Connor, 1998; Dietz, 2003).

Together, these results indicate that a use-dependent plasticity exists in the human spinal cord and is influenced by descending input and somatosensory (both extroceptive and proprioceptive) feedbacks. During locomotion, theses input are known to be mediated via central pattern generators by which rhythmic activities are generated (Dietz, 2003; Zehr, 2005). Spinal reflexes are shown to express acute or chronic plasticity in response to rhythmic movement. Therefore, reflex studies have been used to provide further evidence for activity-dependent plasticity of the human spinal cord.

Rhythmic movement can induce plastic changes in excitability of spinal reflexes

Reflex modulations (i.e. rapid adjustments) are considered an acute form of spinal plasticity (Enoka, 2002; Zehr, 2006). During rhythmic movement, these reflexes are shown to alter in a task- and phase- dependent manner (Stein & Capaday, 1988; Zehr & Stein, 1999). Soleus H-reflex amplitude decreases significantly when changing posture from lying, to sitting, to standing (i.e. task dependency) (Angulo-Kinzler, Mynark, & Koceja, 1998; Goulart, Valls-Sole, & Alvarez, 2000). Also, during walking, soleus H-reflex is smallest during the swing phase of walking and largest during late stance phase (i.e. phase dependency) (Capaday & Stein, 1986). Similar to the H-reflex, cutaneous

reflexes are modulated throughout the human step cycle (Yang & Stein, 1990; Duysens, Trippel, Horstmann, & Dietz, 1990; Zehr, Komiyama, & Stein, 1997).Following a 20 ms train of electrical pulses applied to the tibial or sural nerve at the ankle, a middle latency response in tibialis anterior muscle changes from excitation during swing to inhibition during the swing to stance transition. These responses are attributed to the functional role of cutaneous feedback during locomotion which is termed the "stumbling corrective response "(Duysens et al., 1990).

Rhythmic movement of the arms or legs has been used as a simplified or "reduced" model of locomotion to study movement induced reflex modulation without the influence of trunk or another limb pair. During cycling, both cutaneous and H-reflexes in arm muscles were found to show strong phase- and task dependent modulation (Zehr & Chua, 2000; Zehr et al., 2003). However, in contrast to H-reflexes, the phase dependency of the cutaneous reflexes is limited to active rather than passive movement. This discrepancy has been attributed to the role of central pattern generators in control of rhythmic movements (Brooke, McIlroy, Staines, Angerilli, & Peritore, 1999; Brooke, Cheng, Misiaszek, & Lafferty, 1995). The authors suggest that these reflex modulations happen in the excitability of the reflex pathway (i.e. interneuronal connections and motoneurons) which are strongly influenced by descending and afferent input.

Furthermore, it has been suggested that the level of presynaptic inhibition (PSI) exerted on Ia fibers could be considered as an underlying neural mechanism to explain the H-reflex modulation induced by movement (Capaday et al., 1986; Morin, Katz, Mazieres, & Pierrot-Deseilligny, 1982; Brooke et al., 1997; Brooke et al., 1995; Brooke, McIlroy, & Collins, 1992). Variations in the soleus H-reflex have been studied during

soleus contractions while walking and compared with those observed during voluntary soleus activation. Despite the identical EMG activities in both situations, the H-reflex pathway is always more facilitated during voluntary contractions than during walking (Capaday et al., 1986; Morin et al., 1982). This suggests that the efficacy of the synaptic transmission between the Ia afferents and the motoneuron can be modulated independent of motoneuronal activity. Comparable to walking, other forms of rhythmic activities such as leg cycling or stepping have been reported to induce phase- and task-dependency of H-reflexes in the leg muscles via PSI. During passive movement, the pathways of H-reflexes of the leg and foot are down-regulated both ipsi- and contralaterally. This highlights the role of somatosensory receptors, likely muscle spindle primary endings in movement-induced attenuation of H-reflex pathway via PSI (Brooke et al., 1997; Brooke et al., 1995; Brooke et al., 1992). Furthermore, the phase and task dependency of spinal reflexes induced by rhythmic movements are suggestive of involvement of central pattern generators (CPG) in presynaptic modulations of H-reflex pathway (reviewed in (Zehr, 2005).

In conclusion, rhythmic movements are capable of inducing acute plasticity in the excitability of human spinal reflex circuitry via PSI which is strongly influenced by descending and afferent input. Most interestingly, the effect of rhythmic movement could persist after termination of movement which is discussed in the following section.

Long term suppression of H-reflex induced by rhythmic movement

As mentioned earlier, reflex modulation can persist beyond the period of intervention (Wolpaw et al., 2001; Aagaard, 2003) which is referred as long term or chronic plasticity. There are a few studies that have shown a prolonged inhibitory effect

on the soleus H-reflex pathway induced by rhythmic leg cycling (Misiaszek, Brooke, Lafferty, Cheng, & Staines, 1995; Motl, Knowles, & Dishman, 2003; Mazzocchio, Kitago, Liuzzi, Wolpaw, & Cohen, 2006). Motle, Knowles, and Dishman (2003) measured soleus H-reflex amplitude before and then 10 and 30 minutes after 20 minutes of active and passive leg cycling, and quiet rest. As a result, the amplitude of the soleus H-reflex reduced by about 25% after both types of cycling and remained suppressed for up to 30 minutes. As the amplitude of the H-reflex was similarly reduced after both modes of cycling, activation of the afferent mechanoreceptors of the exercising leg muscles, rather than central motor command signals, was suggested to contribute to the prolonged attenuation of the soleus H-reflex amplitude. Reciprocal inhibition caused by activation of Ia afferents from the anterior tibialis, inhibitory effects from other heteronymous muscles, or prolonged homosynaptic depression between the Ia afferents and alpha motoneurons have been suggested as other possible somatosensory inputs involved in prolonged suppression of H-reflex (Motl et al., 2003). Furthermore, it was shown that one revolution of passive leg cycling (10 rpm) can lead to H-reflex suppression for 1-4 s depending on the phase of cycling (Misiaszek et al., 1995). Authors suggest that during and long after passive leg cycling, there is inhibition of the soleus H-reflex that is not influenced by the level of excitability of the motoneuron pool and is instead likely related to presynaptic inhibition (Misiaszek et al., 1995). As subjects' ankles were kept still in a brace, the presynaptic inhibition is likely attributed to heteronymous connections rather than homosynaptic post-activation depression (Brooke et al., 1997).

Accordingly, it is suggested that rhythmic movement could cause long term adaptations in the H-reflex pathway which is ascribed to the proprioceptive inputs from soleus muscle or heteronymous effect from other leg muscles. However, role of CPGs as the main mechanism generating rhythmic movement is still unclear.

Remote rhythmic movement can induce acute adjustments in spinal reflexes

Remote rhythmic movement (i.e. arm movement while reflexes are recorded in the legs or vice versa) can induce acute plasticity of spinal reflexes. These reflex modulations are attributed to the interlimb coupling between arms and legs which is required for coordinated locomotion (Dietz, 2002; Zehr, 2005).

It has been suggested that CPGs at the cervical and lumbosacral levels communicate during locomotion and make use of interlimb reflex pathways for coordinated movement (Guadagnoli, Etnyre, & Rodrigue, 2000; Zehr, 2005). It has been shown that arm movements during walking are caused by the muscular activity and not passive pendular movement (Jackson, 1983). In fact, even with the arms restrained, there is still rhythmic arm muscle activity during natural walking (Fernandez-Ballesteros, Buchtal, & Rosenfalck, 1965). It was later reported that inter limb coordination in human is of a 1/1 frequency locked relationship in walking and creeping. In swimming, this frequency relationship decreased as the rate of swimming increased; however, the coordinated movement between limb pairs was preserved (Wannier, Bastiaanse, Columbo, & Dietz, 2001). These observations are considered as evidences for interlimb coupling during locomotor tasks. Recently, Balter and Zehr (2007) used the modulation of cutaneous reflexes to probe the neuronal coupling between the arms and legs during arm and leg cycling. They found that there is an interaction of rhythmic arm and leg

movement so that full expression of the effect of rhythmic arm movement is observed only when both the arms and legs are moving.

Remote rhythmic movement has been shown to induce acute adjustments of H-reflex excitability via interlimb coupling. During rhythmic movements of one foot, H-reflexes in forearm flexor muscles are modulated phase-dependently (Baldissera, Cavallari, & Leocani, 1998). Interestingly, whole leg cycling results in generalized suppression of H-reflexes in forearm muscles (Zehr, Klimstra, Johnson, & Carroll, 2007). Also, passive movement at the elbow joint facilitates soleus H-reflexes (Hiraoka & Nagata, 1999) whereas H-reflexes were inhibited by rhythmical arm swings or cycling (Hiraoka, 2001; Frigon et al., 2004; Loadman et al., 2007). The general suppression of soleus H-reflexes induced by remote rhythmic movement could be increased by doubling cycling rate and range of arm movement (Loadman et al., 2007). These studies show that H-reflex amplitudes express acute adaptive plasticity in response to remote movement signals and can be modified by movement parameters such as rate and range.

The H-reflex plasticity induced by remote movement is also influenced by cutaneous feedbacks. During arm cycling, Frigon et al. (2004) used sural and common peroneal (CP) nerves stimulation by which soleus H-reflexes were facilitated and inhibited, respectively. It has been also shown that superficial radial (SR) nerve stimulation facilitates the soleus H-reflex in static position and counteracts the suppressive effect of arm cycling (Zehr et al., 2004). However, interlimb cutaneous reflexes (SR) are not modulated by remote cycling movement with stationary legs (Zehr et al., 2004). The authors suggest that arm cycling does not affect the soleus H-reflex pathway at a point that is common with the cutaneous reflex pathway (i.e. motoneuron),

but affects the H-reflex excitability via presynaptic inhibition of the Ia afferent pathway. Recent studies have further established the role of PSI as the main control mechanism associated with H-reflex modulation during remote rhythmic movement (Frigon et al., 2004; Loadman et al., 2007; Zehr et al., 2007).

In summary, remote rhythmic movement induces an acute suppression of H-reflex amplitude. This suppression can be influenced by movement parameters and also, cutaneous feedback from the upper or lower limbs. However, whether conditioning by remote movement can induce long term plasticity of the H-reflex pathway has remained unclear. This will be the main focus of the second chapter of this thesis.

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CHAPTER 2: MANUSCRIPT

Introduction

Plasticity in the motor system is a topic of increasing interest and refers to the capability of the central nervous system (CNS) for compensatory adaptations for motor skill learning and recovery after damage (Wolpaw & Tennisen, 2001). Reflexes have been used to explore spinal plasticity by examining changes in excitability in response to different interventions. Reflex amplitudes are amenable to plastic adaptation following exercise or activity (Wolpaw et al., 2001; Aagaard, 2003; Wolpaw & Carp, 2006; Zehr, 2006). The Hoffmann (H-) reflex has been a useful tool for experiments in both reduced animal and intact human preparations in this regard.

Movement is a powerful modulator of reflex amplitudes and the effect of both active and passive movement on the modulation of H-reflexes within a limb has been well demonstrated. Leg movements occurring during stepping, cycling, or walking can induce strong suppression of H-reflex amplitude (Brooke, Cheng, Misiaszek, & Lafferty, 1995; Capaday & Stein, 1987). Also, "remote" movement (i.e. arm movement while reflexes are recorded in the leg or vice versa) can affect the excitability of H-reflex spinal circuitry. Interestingly, as with leg movement, arm cycling attenuates soleus H-reflex amplitude in stationary legs (Frigon, Collins, & Zehr, 2004). This attenuation can be increased by doubling cycling rate and range of arm movement (Loadman & Zehr, 2007). The main mechanism leading to modulation of soleus H-reflex amplitude during leg or arm movement is presynaptic inhibition (PSI) of Ia

afferent transmission (Brooke et al., 1995; Frigon et al., 2004; Zehr, Hoogenboom, Frigon, & Collins, 2004).

Some evidence suggests that the immediate effect of rhythmic movement on reflex amplitude can persist beyond the period of movement conditioning (Misiaszek, Brooke, Lafferty, Cheng, & Staines, 1995; Motl, Knowles, & Dishman, 2003; Mazzocchio, Kitago, Liuzzi, Wolpaw, & Cohen, 2006). For example, after passive leg cycling, H-reflex amplitude remained significantly suppressed for up to 4 s after cycling terminated (Misiaszek et al., 1995). Another study found that twenty minutes of active and passive leg cycling could lead to suppression of soleus H-reflex amplitude that could last for 30 minutes after cycling stopped (Motl et al., 2003). These findings suggest leg movement can induce short-term plasticity of H-reflexes in the leg muscles that persists beyond the period of conditioning. However, it remains to be investigated if remote movement can also have long lasting effect on the H-reflex circuitry. Therefore, the first objective of this study was to test the hypothesis that arm cycling, a remote conditioning effect, could produce prolonged suppression of the soleus H-reflex.

The H-reflex suppression induced by remote movement is influenced by cutaneous feedback. During arm cycling, Frigon et al. (2004) used sural and common peroneal (CP) nerve stimulation by which soleus H-reflexes were facilitated and suppressed, respectively. Interlimb cutaneous reflexes could also contribute to motor coordination between the arms and legs during motor tasks such as walking (Haridas & Zehr, 2003). It was shown that cutaneous nerve stimulation at the wrist (superficial radial; SR) could evoke interlimb reflexes in many leg muscles during sitting (Zehr, Collins, & Chua, 2001), and walking (Haridas et al., 2003). It has been also shown that

SR nerve stimulation facilitates the soleus H-reflex in static positions and counteracts the suppressive effect of arm cycling (Zehr et al., 2004). In contrast to rhythmic movement, SR cutaneous inputs reduce the presynaptic inhibition of the Ia afferent-alpha motoneuronal pathway (Zehr et al., 2004). Thus, the second objective of the present study was to test the hypothesis that remote cutaneous input evoked by SR nerve stimulation would interfere with any prolonged suppressive effect of arm cycling on soleus H-reflex amplitude.

Methods

Subjects

Thirteen subjects (aged 22 to 43 years; 8 females and 5 males) with no history of neurological disorders were recruited in this study. Participants provided informed written consent in a protocol approved by the Human Research Ethics Committee at the University of Victoria and in accordance with the declaration of Helsinki.

Protocol

The experimental methodology and protocol are similar to that described in previous experiments involving arm cycling (Zehr & Chua, 2000; Zehr & Kido, 2001; Zehr, Collins, Frigon, & Hoogenboom, 2003; Frigon et al., 2004; Loadman et al., 2007). Participants were seated in a custom adapted chair with support provided for their trunk and legs. The feet of each subject were fixed to foot plates and a neutral ankle angle (~ 90 degrees) was set. Unwanted movements in the trunk and lower limb were minimized. A custom-made (Z. Kenwell, University of Alberta) hydraulic arm ergometer (described in (Zehr et al., 2003) was positioned directly in front of the

subjects. Subjects were asked to hold the handgrips firmly but comfortably (with the forearms pronated) and perform 30 minutes of rhythmic arm cycling while maintaining a relaxed posture in the rest of the body. The handles of the ergometer were constrained to move together but were 180 degrees out of phase. Arm cycling was performed in a clockwise direction (viewed from the right side of the body) in which the 3 o'clock position corresponded to the largest extended elbow angle and maximal shoulder flexion (~70° in front of the mid-axillary line). Lastly, participants cycled at a comfortable pace (~60 rpm) and were provided with visual feedback on an oscilloscope (Hameg 20MHz, HM205-3, Frankfurt/Main, Germany) displaying cycling frequency.

Two sets of experiments were conducted both involving arm cycling and static (pre- and post-cycling) trials. In experiment I (subject n=12), the prolonged effect of arm cycling on soleus H-reflex amplitude was investigated. In experiment II (n=8), cutaneous (SR nerve) conditioned H-reflexes were evoked after each unconditioned H-reflex test in static trials to evaluate the interaction of arm cycling with cutaneous input after termination of movement. Experiment II was conducted after experiment I once the H-reflex amplitudes returned to the control values. For three subjects, experiment II was performed on a different day from experiment I. An additional control experiment was conducted with identical protocol to the first experiment except that subjects (n=4) did no cycling.

H-reflex stimulation

To evoke H-reflexes in the soleus muscle, the tibial nerve was stimulated with single 1 ms square wave pulses at the left popliteal fossa using bipolar surface electrodes (Thought Technologies Ltd.) and a Grass S88 stimulator (Grass Instruments,

AstroMed Inc.) connected in series with a Grass SIU5 isolation unit and a CCU1 constant current unit. Nerve stimulation was delivered pseudo-randomly between 3 and 5 seconds apart when the hand ipsilateral to the stimulation was at 3 o'clock (as described above).

At the beginning (i.e. pre-cycling period) of both experiments, H-reflex and M-wave recruitment curves (RCs; n=40 sweeps) were constructed to determine the maximum M-wave (M_{max}; mean of three largest M-wave values) and maximum H-reflex sizes (H_{max}). Subsequently, stimulation intensity was set to evoke an H-reflex size of 70-80% of H_{max} on the ascending limb of the recruitment curve. This position corresponded to an M-wave size of ~ 3% of M_{max}. This M-wave amplitude was monitored and adjusted on line to assure consistent stimulation intensity. Current was measured by a mA-2000 Noncontact Milliammeter (Bell Technologies, Orlando, FL).

In addition to two RCs at the beginning and end of both experiments, two more RCs (30 sweeps) were recorded at one minute after start and end of cycling in experiment I. RCs were used to determine M_{max} amplitudes to normalize data (see data analysis) and control the consistency of M_{max} over the course of the experiment.

SR nerve stimulation

In experiment II, a conditioning paradigm was added to the static trials of the first experiment so that each post-cycling H-reflex was followed by an H-reflex conditioned with SR nerve stimulation. A condition-test (C-T) interval of 100 ms was used (Zehr et al. 2004). Cutaneous nerve stimulation made use of the same stimulator instrumentation as for the H-reflexes except that trains of 5×1.0 ms pulses at 300 Hz were delivered to the SR nerve. Flexible electrodes (Thought Technologies Ltd) for SR nerve stimulation were

placed on the dorsal surface of the forearm just proximal to the radial head and the crease of the wrist joint. Stimulus intensity was set at twice the threshold at which a clear radiating paresthesia (radiating threshold, RT) into the innervation area of the nerve (dorsal surface of the hand towards the index finger and thumb) was reported (Zehr et al., 2001; Haridas et al., 2003).

Electromyography (EMG)

EMG was recorded with surface electrodes (Thought Technologies Ltd.) in bipolar configuration. The ground electrode was placed on the patella bone. The soleus, tibialis anterior (TA), vastus lateralis (VL), biceps femoris (BF), and anterior deltoid (AD) muscles were recorded ipsilateral to H-reflex stimulation. The pre-stimulus (20ms) EMG from each muscle was used to determine the level of background muscle activation at the time of reflex sampling. For soleus, EMG signals were pre-amplified at 500 Hz and band pass filtered 100-1000 Hz (P511 Grass Instruments, AstroMed Inc.). For the other muscles, EMG was amplified by 5000 times, band pass filtered 100-300Hz and full-waved rectified.

Data acquisition and analysis

In both experiments, H-reflexes were evoked at 5 minute intervals, starting prior to cycling, continuing throughout the 30 minute cycling period and up to 30 minutes after cycling termination. In experiment II each H-reflex test was followed by an SR conditioned H-reflex for all the static trials.

Data were sampled at 5000 Hz with a 12- bit A/D converter controlled by a custom-written Labview (National Instruments, Austin, Tx. USA) computer program.

For all the trials, 10 sweeps (70 ms duration) were collected. Peak-to-peak amplitudes of M-waves and H-reflexes were determined off-line (custom-written software, Matlab, Nantick) from the single sweeps of soleus EMG and were averaged and normalized to the M_{max} values (see below) to reduce inter-subject variability (Frigon et al., 2004). In experiment I, data were normalized to the corresponding M_{max} obtained from the RC which was within 20 minutes of sampling. In experiment II, data were typically normalized to the average M_{max} from the beginning and end of the experiment.

Statistics

In both experiments, STATISTICA (StatSoft, Tulsa, OK, USA) was used to perform repeated measures analysis of variance (ANOVA) to identify significant main effects for time intervals on the amplitudes of the soleus H-reflexes, M waves, and prestimulus EMG levels. The mean amplitudes of the H-reflexes prior to cycling were used for the control values (H-control). In experiment I, a two-tailed paired t-test was used to compare the H-reflex amplitude averaged across cycling trials with the average from the post-cycling trials. In both experiments I and II, Dunnett's *post hoc* test was used to compare mean values of H-reflex amplitudes from each cycling and post-cycling trial with H-control. For experiment II, control values of the H-reflex and conditioning test were compared using two-tailed paired t-tests. To confirm that the conditioning of reflex amplitude induced by arm cyling was similar in the two experiments, two-tailed paired t-tests were used to compare H-reflex amplitudes in experiment I at different time intervals (pre-cycling, cycling ,and the first post-cycling trials) with those in experiment II across subjects who participated in both experiments

(n=7). Finally, for the background EMG, M-wave, and M_{max} values, Tukey's HSD *post hoc* tests were applied. Statistical significance was set at $p < 0.05$.

Results

Experiment I: Prolonged effect of arm cycling on soleus H-reflex amplitude

The effect of prolonged arm cycling on H-reflex amplitude is shown in Figure 1 for a single subject at pre-cycling, 5 minutes of cycling, and 10 min post-cycling. H-reflex amplitudes were significantly decreased during cycling ($p< 0.001$) and remained suppressed up to 20 minutes after cycling termination ($p \leq 0.04$). In Figure 2, group data are shown for H-reflex amplitudes evoked during (solid bars) and after (dashed bars) cycling. The H-control amplitude is shown as the solid horizontal line. Despite similar M-waves and background EMG levels (not shown), H-reflex amplitudes were significantly reduced during cycling and remained suppressed for up to 20 minutes after cycling ended. Arm cycling caused a sudden attenuation of H-reflex amplitudes by ~18 % ($p < 0.001$). This is shown in the ten individual sweeps labeled as "1st min cycling" in Figure 3. On this figure the individual sweeps recorded during one minute after termination of cycling show a gradual trend increasing by ~ 6 % which was still significantly different from H-control. This is shown by the dashed bars presenting the first ten sweeps after termination of cycling in Figure 3. It was also shown that the average suppression of H-reflex amplitudes during cycling and 20 minute afterwards were not significantly different from each other.

In experiment I, there were no significant differences for soleus, TA, VL, and BF EMG levels across the different time intervals. AD background EMG was not significantly different among various time intervals in static trials (except at zero after cycling, $p < 0.001$). Pre-cycling M_{max} values were found to be significantly different from those obtained during and after cycling. However, since the H-reflexes were

normalized to temporally corresponding M_{max} amplitudes, any potential confounding effect was mitigated.

Experiment II: Effect of SR stimulation on prolonged suppression of soleus H-reflex amplitude

In this part of the experiment, SR conditioning of H-reflexes was applied immediately after each H-reflex test during the post-cycling period. Thus, the first H-reflex trial immediately after cycling (i.e. zero @ post-cycling) was not preceded by any SR conditioning. H-reflex amplitudes were significantly decreased during cycling. As is shown in Figure 4, H-reflex amplitudes remained suppressed only for the first H-reflex trial after cycling termination (see asterisk on Figure 4). H-reflex amplitudes subsequent to the initial application of SR stimulation were no longer significantly suppressed relative to control amplitude.

Comparison of experiment I to II at different time intervals showed that averaged H-reflex amplitudes were not significantly different at control, cycling, and the first post-cycling trials. Therefore, the earlier recovery of the H-reflexes to control amplitude seen in experiment II is attributed to the cutaneous input as applied with SR stimulation.

The size of the SR conditioned control H-reflexes (i.e. amplitude of conditioned H-reflex by SR before cycling) was significantly larger than H-reflex control ($p < 0.001$), indicating significant facilitation of the H-reflex pathway due to cutaneous conditioning. As is shown in Figure 5, SR conditioning tests did not show any significant change from pre- to post-cycling period.

For background muscle activity in experiment II, there was a main effect for soleus EMG. However, further Tukey's HSD *post hoc* showed no significant difference

except for at 15 min of cycling compared with 25 min of post-cycling. Also, no significant differences were found for TA, BF and AD muscles. There were small differences in background EMG of VL muscle but it was always less than one microvolt. M_{max} amplitudes were not significantly different across this experiment.

Control study: Effect of number of stimuli and time course on the H-reflex size

As shown in Figure 6, H-reflex amplitudes did not change significantly when participants did no cycling. Also, levels of background EMG, M-wave and M_{max} amplitudes were not significantly different.

Discussion

The main finding of this study is that the suppressive effect of arm cycling on soleus H-reflex amplitude persists beyond the period of cycling. These findings support the working hypothesis that interlimb coupling between arms and legs affects neuronal circuitry that can express long lasting changes in the excitability of the H-reflex pathway. Furthermore, it was found that the adaptive plasticity of the H-reflex pathway is strongly influenced by remote cutaneous volleys.

Methodological Considerations

In the present study, the amplitude of the direct motor response (M-wave) was kept constant to assure similar stimulus input to the tibial nerve and therefore consistent activation of the Ia afferents (Brooke et al., 1997; Zehr et al., 2003). H-reflex and M-wave amplitudes were normalized to the M_{max} to reduce inter-subject variability (Zehr, 2002). However, the amplitude of M_{max} may vary in the relaxed muscles during the course of an experiment (Crone, Johnsen, Hultborn, & Orsnes, 1999). To minimize the effect of minor M_{max} variations such as we experienced, H-reflex and M-wave values were normalized to data from RCs recorded within 20 minutes of H-reflex sampling. Our results showed that changes in M_{max} did not significantly affect the size of M-waves or stimulus input over the course of the experiment. Therefore, it is improbable that prolonged H-reflex suppression was due to a change in the afferent volley used to evoke the reflex.

To control the possible effects of heteronymous muscle activity on the soleus H-reflex pathway (Meunier, Pierrot-Deseilligny, & Simonetta, 1993; Iles & Roberts, 1987), participants were seated in a chair equipped so that the trunk and lower limb joints were supported to prevent any perceptible movements. There were no differences

in the background EMG of the leg muscles across experimental trials. Furthermore, as vestibular and neck receptors as well as mental state can influence the H-reflex response (Schieppati, 1987), each subject was instructed to keep their head in a neutral position during the experiment.

Previous activation of Ia afferents may cause a depression in the H-reflex amplitude which may last from a few milliseconds to several seconds (Sabbahi & Sedgwick, 1987; Rossi-Durand, Jones, Adams, & Bawa, 1999). We used pseudo-random stimulus intervals of 3-5s to avoid any such prolonged effects from previous activation of the test pathway (Sabbahi et al., 1987). Importantly, the lack of H-reflex attenuation in the control study with no arm cycling demonstrates that any effect of repetitive activity in the H-reflex pathway was insignificant. Thus, we are confident that arm cycling and not methodological issues, was responsible for the prolonged suppression of H-reflex amplitude shown here.

Remote movement induces prolonged suppression of H-reflex circuitry

The main finding of this study is that the suppressive effect of arm cycling on the soleus H-reflex pathway persists after termination of cycling. This suggests that remote movement signals are capable of inducing prolonged changes in the excitability of this pathway. It has previously been shown that during rhythmic movement of one limb pair (arms or legs), the opposite stationary limb pair (legs or arms) shows a general suppression of H-reflex excitability (Frigon et al., 2004; Loadman et al., 2007; Zehr, Klimstra, Johnson, & Carroll, 2007). Suppression of soleus H-reflex amplitude has been attributed to reinforcement of segmental Ia presynaptic inhibition during arm cycling

(Frigon et al., 2004; Loadman et al., 2007). In the present study, soleus H-reflex amplitudes were suppressed during arm cycling, consistent with the previous findings.

The prolonged effect of remote movement on H-reflex excitability has not been studied before. However, there is some evidence that supports activity–induced plasticity of soleus H-reflex amplitudes following leg cycling (Motl et al., 2003; Misiaszek et al., 1995). After one revolution of slow (10 rpm) passive leg cycling, soleus H-reflexes remained suppressed up to 1-4s after cessation of movement while tonically maintained background EMG did not significantly change. This suggests that the H-reflex was suppressed via changes in PSI during cycling and also after termination of movement (Misiaszek et al., 1995). Here, we did not have subjects maintain a constant level of contraction as it was impossible to sustain such contraction for 30 minutes. Background EMG in the rested leg muscles was shown to be consistent during the post-cycling period. Since arm cycling induces a generalized suppression of H-reflex amplitude via the modulation of Ia PSI (Frigon et al., 2004; Loadman et al., 2007), we suggest the simplest explanation of our results here to be that this effect extends over the post-cycling period. It should be noted that this is not likely to be some general systemic effect of arm cycling exercise. Motl and Dishman (2003) showed that prolonged leg cycling suppressed only H-reflexes in the leg muscle soleus that was activated and not the flexor carpi radialis in the arm that was at rest. This strongly argues against a systemic or hormonal effect.

Although the mechanism which leads to the persistence of Ia PSI remains unclear, the present findings include some features that suggest plateau-like behavior of interneurons mediating Ia PSI. Plateau potentials could generate self-sustained firing

that would lead to persistent activity in this pathway (Hounsgaard, Hultborn, Jespersen, & Kiehn, 1988; Gorassini, Bennett, & Yang, 1998; Kiehn & Eken, 1997; Collins, Burke, & Gandevia, 2001; Collins, Burke, & Gandevia, 2002). Thus, sustained suppression of H-reflex amplitude could occur with sustained activity of the Ia pre-synaptic inhibitory interneuron.

Cutaneous stimulation cancels out the movement- induced plasticity of H-reflex

After termination of cycling, cutaneous nerve stimulation immediately returned H-reflex amplitudes to control levels (see Figure 4). This is in line with our previous study in which SR nerve stimulation significantly facilitated H-reflex amplitudes during static contractions and counteracted the suppression of reflex amplitude induced by arm cycling (Zehr et al., 2004). In the present study, after application of SR stimulation, unconditioned H-reflex size was not significantly different from control value and it returned completely to the control size after 15 minutes. As plateau-like behavior is shown to be terminated by such inputs (Lee & Heckman, 1998), we speculate that SR stimulation was able to cancel plateau-like behavior of the Ia presynaptic inhibitory interneuron. Interestingly, there were no significant changes in the amplitudes of H-reflexes conditioned by SR stimulation after termination of cycling (Figure 5).Therefore the modulation of transmission of volleys from afferents in the cutaneous SR nerve to the Ia afferent soleus motoneuronal terminals was not influenced by the prolonged effect of rhythmic movement. This is shown in Figure 7 in a model modified from an earlier study (Frigon et al. 2004). In this model, pathways from the SR nerve and remote movement signals share the last order interneuron onto the Ia presynaptic pathway. Arm cycling suppresses H-reflex size by increasing Ia PSI during arm cycling. The activation of

plateau potentials and presumed interneuronal bistability in this pathway is shown as a dotted arrow. In contrast, SR stimulation facilitates the H-reflex pathway via reducing Ia PSI. The simplest explanation is that this remote cutaneous input turns off the plateau potential behavior. Plateau potentials have been described in many central neurons (Fraser & MacVicar, 1996; Morisset & Nagy, 1999) and have been well verified in mammalian motoneurons (Bennett, Hultborn, Fedirchuk, & Gorassini, 1998; Kiehn & Eken, 1998; Collins et al., 2001; Collins et al., 2002). Our results suggest the existence of such behavior at interneuronal levels in the human. This is in agreement with previous findings in some classes of spinal interneuron in the ventral horn of the turtle (Hounsgaard & Kjaerulff, 1992) and the dorsal horn of rats, and turtles (Morisset & Nagy, 1996; Russo & Hounsgaard, 1996).

Functional implications

The results of the present study have functional implications for incorporating rhythmic arm movements in locomotor retraining strategies. It has been previously suggested that there is a flexible neural coupling of the upper and lower limbs which allows for interlimb coordination during locomotor tasks such as walking in healthy (Zehr & Duysens, 2004; Zehr, 2005) and neurologically impaired populations (Behrman & Harkema, 2000; Ferris, Huang, & Kao, 2006). One experimental functional outcome of these pathways is the suppression of soleus H-reflexes during arm cycling. The current results now demonstrate the capacity for these pathways to express short-term neural plasticity. This is an essential feature which would permit a prolonged effect of any related rehabilitative interventions. Most importantly, the result of the present study might be useful in mitigation of spasticity. Muscle spasticity is caused by exaggerated

reflex excitability after CNS disorders such as stroke (Pierrot-Deseilligny, 1990) and is correlated with H-reflex size in the neurologically impaired population (Levin & Hui-Chan, 1993). Since rhythmic arm movement can produce sustained suppression in the soleus H-reflex pathway, it could be proposed as a helpful therapeutic tool for altering spasticity. This is in line with an observation in spastic patients that arm swing (associated with harness supported stepping) caused greater and more symmetric muscle activation (Visintin & Barbeau, 1994; Ferris et al., 2006). However, additional work remains to determine if rhythmic arm movement can still effectively access neural coupling between arms and legs and induce a prolonged suppressive effect on the H-reflex pathway in the neurologically impaired population.

Figures

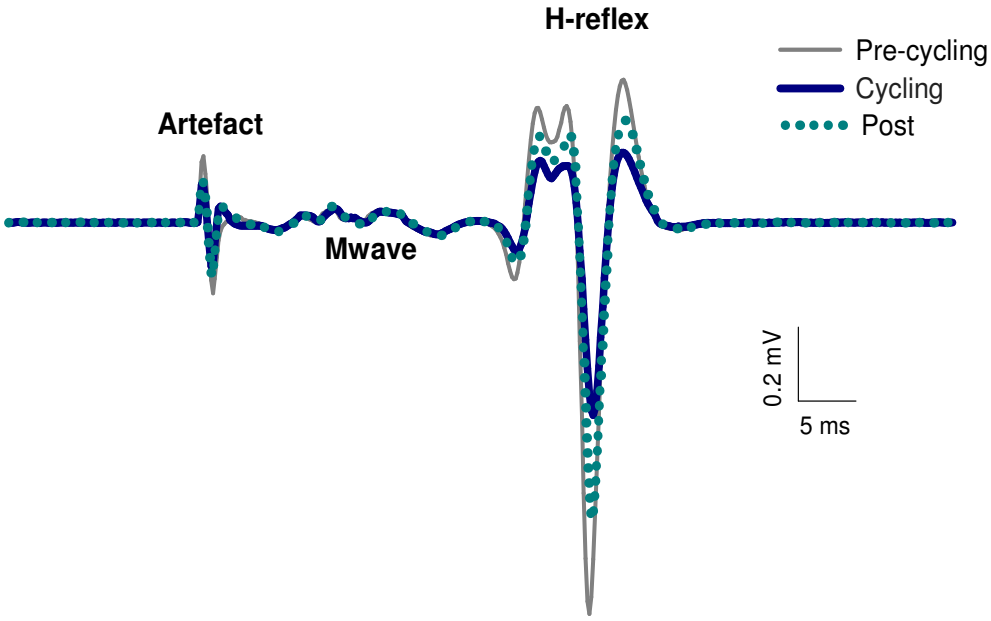

Figure 1: **Long-lasting suppression of soleus H-reflex amplitude induced by arm cycling in a single subject.** Data are averages of 10 sweeps recorded at pre-cycling (control; gray line), cycling (5 minutes; black line) and post (10 minutes after termination of cycling; dotted line) periods. Stimulus artifacts, M-waves, and H-reflex are indicated.

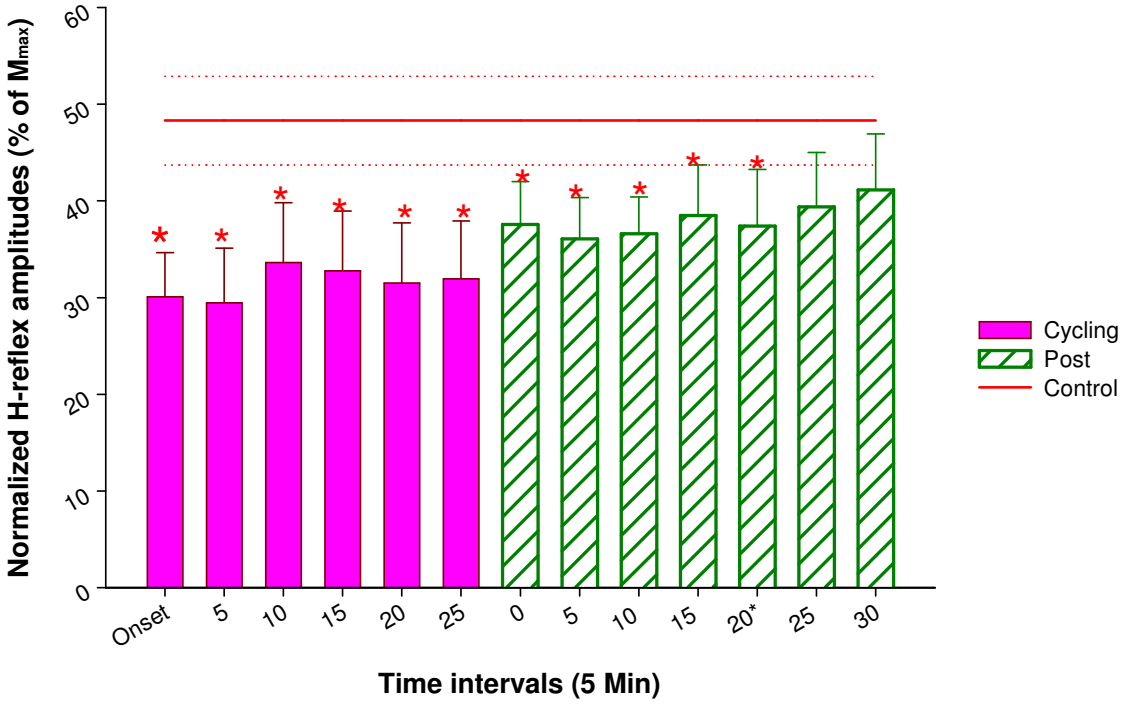

Figure 2: **Prolonged effect of arm cycling on H-reflex amplitude**. Cycling (dark bars) and post (post-cycling; dashed bars) H-reflex amplitudes are compared to pre-cycling or control amplitudes (horizontal solid line). The time "0" in the post-cycling period indicates recordings of 10 sweeps of H-reflexes taken immediately after termination of cycling. Values are mean across all participants (n=12) ± (SEM).The horizontal dotted lines are one standard error of the mean (SEM) for the control reflex size. (*) denotes significant differences between H-reflex amplitude recorded during cycling and up to 20 minutes post-cycling compared with the control H-reflex size.

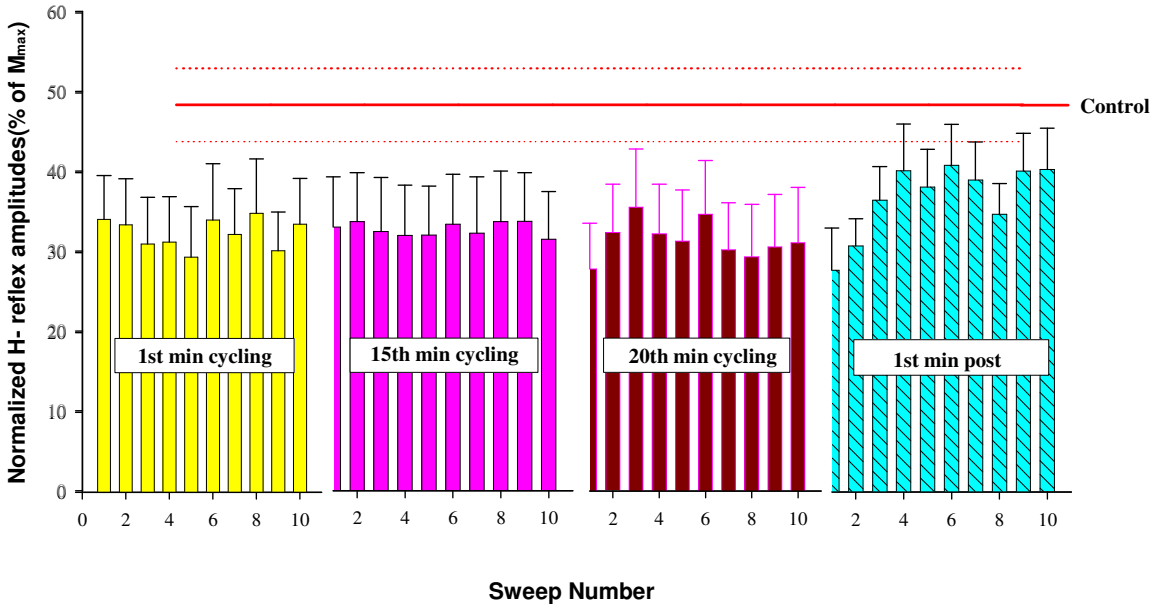

Figure 3: **Display of 10 individual sweeps at different time intervals during (1, 15, and 20 minutes) cycling and from the first minute post-cycling.** Arm cycling caused a sudden attenuation of H-reflex amplitude (1st min cycling) but a gradual increase after termination of cycling (1st min post). Values are means across all participants (n=12) ± (SEM).

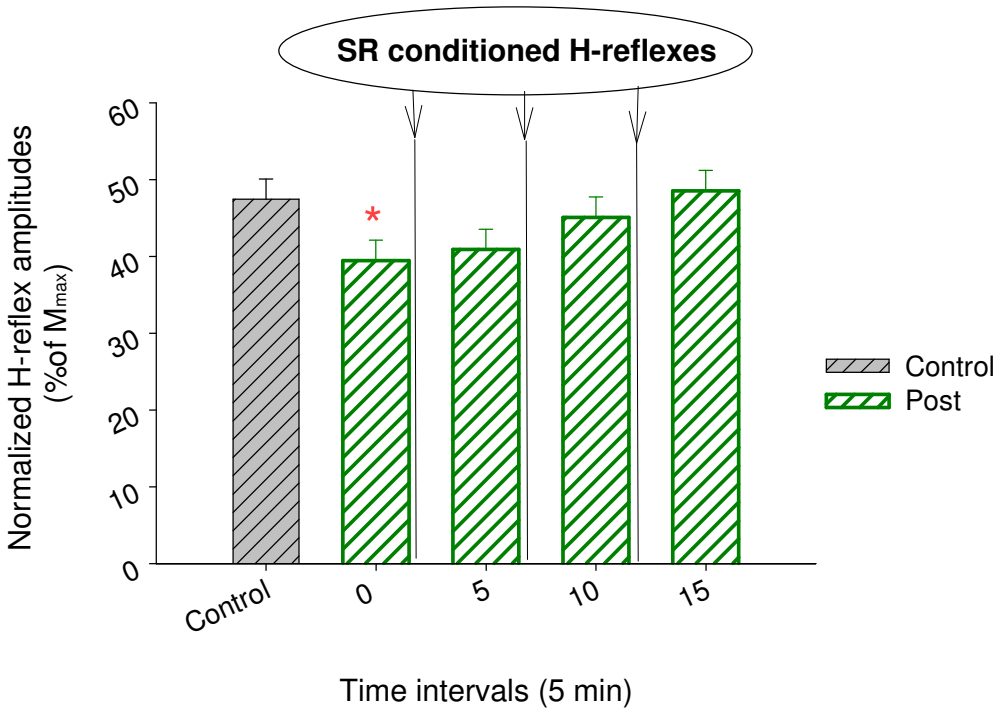

Figure 4: **H-reflex suppression after arm cycling termination when combined with SR conditioning.** Arrows show the temporal sequence of SR conditioned H-reflexes in regards to unconditioned H-reflexes (dashed bars). H-reflex amplitudes (light bars) are compared to H-reflex amplitude recorded prior to cycling (Control; gray bar). Values are means across all participants (n=8) ± (SEM). (*) denotes significant difference between H-reflex amplitudes recorded at zero minute post-cycling with the control H-reflex size.

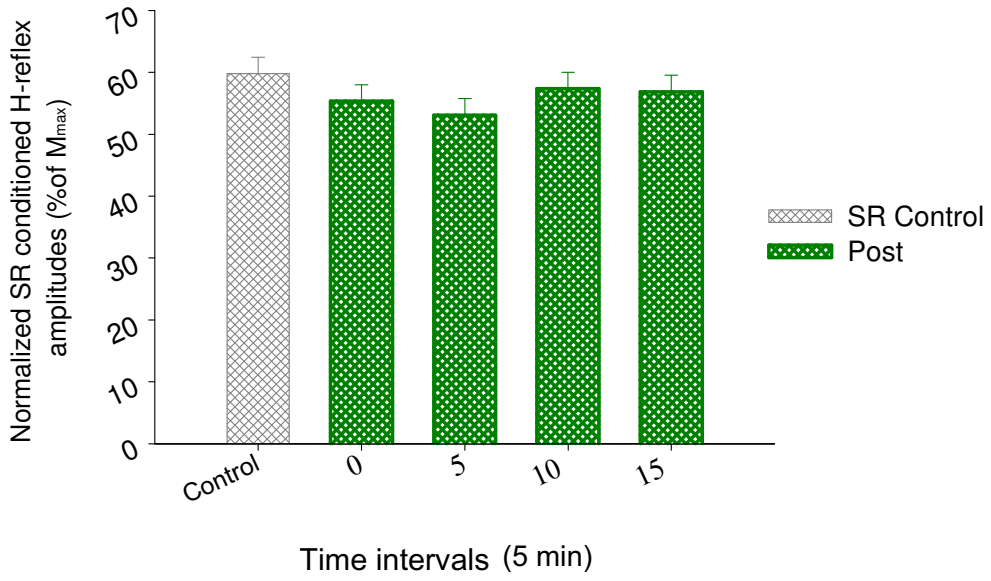

Figure 5: **Conditioned H-reflex amplitudes after termination of arm cycling compared with pre-cycling.** SR conditioned H-reflexes after arm cycling (post; dark bars) are compared to those evoked prior to cycling (SR Control; gray bar). Values are means across all participants (n=8) ± (SEM). No significant differences were observed.

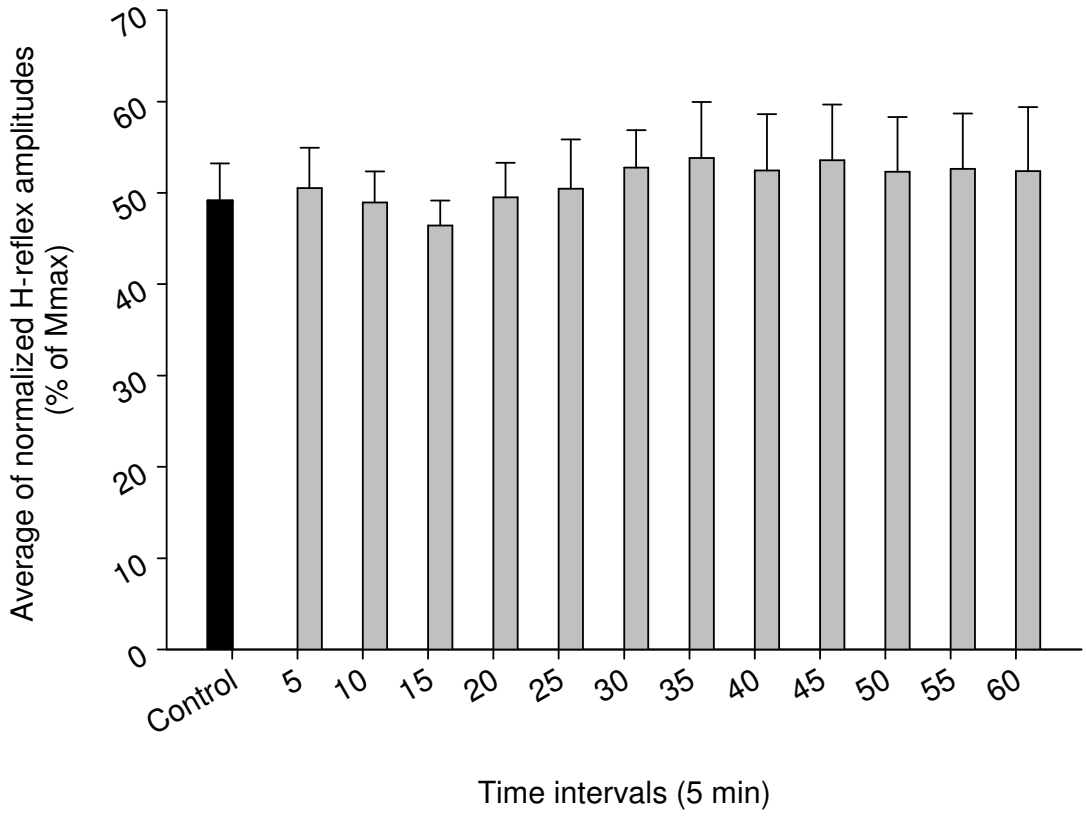

Figure 6: **H-reflex amplitudes are unchanged during the control experiment with no cycling.** H-reflex amplitudes at different time intervals (dark bars) compared to control size (defined as the very first H-reflex amplitude and shown as the first bar).Values are mean across all participants (n=4) ± (SEM). There is no significant difference.

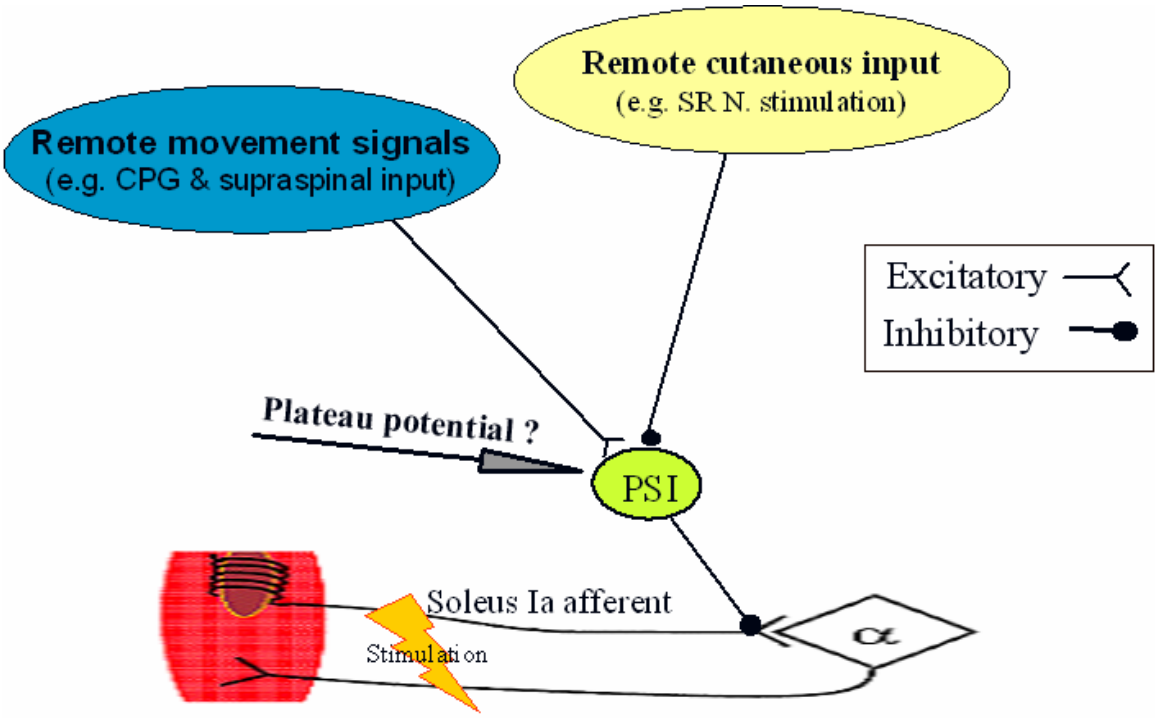

***Figure 7*: Possible pathways that influence soleus Ia presynaptic inhibition.** Excitatory and inhibitory connections are shown with an open triangle and a filled black circle, respectively. At the bottom is a simplified H-reflex pathway from primary muscle spindles (group Ia) synapsing with α-motoneurons of the soleus. PSI changes the excitability of this pathway. PSI is influenced by remote movement signals and cutaneous pathways. Arm cycling activates the pathway by which H-reflex size is suppressed. The plateau potential effect of prolonged arm cycling on presynaptic inhibitory interneuron is shown as gray arrow. SR stimulation is postulated to inhibit the presynaptic inhibitory interneuron and turns off the plateau potential effect of prolonged arm cycling. This explains why H-reflex sizes recover immediately after application of SR stimulation. **Abbreviations:** Central Pattern Generator (CPG), Superficial Radial Nerve (SR N.), Presynaptic Inhibition (PSI), Alpha-motoneurons (α).

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