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Elizabeth A. Arnold April 11, 2016

Downslope walking and the H-reflex pathway: dose-response effect and generalizability

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An abstract of
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Abstract

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The purpose of this study was to determine whether downslope treadmill walking reduces spinal excitability in a dose-dependent manner. Soleus (Sol) and tibialis anterior (TA) H-reflexes were measured in twelve neurologically intact adults on four or five days. Measurements were taken before and after four downslope walking (DSW) doses (10 minutes at -15%, 20 minutes at -15%, 10 minutes at -25%, 20 minutes at -25%) at 2.5 mph, and eight participants also completed level walking (LW) for 20 minutes. To obtain the Sol and TA H-reflex and M-wave recruitment curves, the tibial nerve (Sol) and common peroneal nerve (TA) were electrically stimulated with a range of stimulus intensities while participants maintained background activity at 20% of maximum Sol and TA activity, respectively. The H-reflex was expressed as the ratio of H_{max} to M_{max}. Recurrent inhibition was measured as the percent difference between the unconditioned H-reflex and conditioned H-reflex. Heart rate (HR) and ratings of perceived exertion (RPE) were measured during walking. DSW for 20 minutes at -15%, 10 minutes at -25%, and 20 minutes at -25% caused greater Sol H_{max}/M_{max} depression than LW (30 ± 21%, 34 ± 23%, 36 ± 22% vs. 15 ± 15%, $P \leq .02$), and DSW for 20 minutes at -25% caused greater H_{max}/M_{max} depression than 10 minutes at -15% (36 ± 22% vs. 18 ± 23%, $P \leq .01$). There was no effect of LW or DSW on TA H-reflexes or recurrent inhibition. HR and RPE were highest during DSW at the -25% slope. In conclusion, DSW causes dose-dependent depression of Sol H-reflexes, but only when comparing the smallest and largest DSW doses, and these effects are not generalizable to the TA.

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Introduction

Spasticity in Neurologically Damaged Individuals

Spasticity is a disabling and chronic disorder experienced by many individuals with neurological impairments. Recent studies have shown that between 20-30% of stroke victims experience spasticity (Sommerfeld et al., 2012). The prevalence is slightly higher for patients with multiple sclerosis (MS), with 34% reporting moderate to severe spasticity, impacting their ability to perform daily activities. Additionally, 50% of MS patients had minimal to mild symptoms (Rizzo et al., 2004). Spinal cord injuries (SCI) are also highly correlated with spasticity. Studies have found that within a year after SCI, 65-78% of individuals report spasticity (Adams and Hicks, 2005).

Spasticity is defined as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motoneuron syndrome" (Lance, 1980). An increase in muscle tone, or passive resistance to stretch, is known as hypertonia. Spasticity is one component of hypertonia. Muscle weakness can also lead to hypertonia, which is known as intrinsic hypertonia. Further, immobilization and prolonged contraction of muscles change soft tissue properties and cause oversensitivity of muscle spindles, which activate the stretch reflex to resist further muscle stretch. An important distinguishing feature of spasticity is velocity-dependence, meaning there is more resistance when the muscle is stretched at a faster rate (Trompetto et al., 2014).

SCI does not immediately cause spasticity. At first, spinal reflexes are nearly impossible to elicit, and gradually, the reflexes become exaggerated. Antigravity muscles, such as leg extensors and arm flexors, are more likely to develop spasticity (Wolpaw and

Tennissen, 2001). Patients with spasticity normally experience hypertonia in one or more muscles, causing problems with gait, fatigue, muscles spasms, muscle stiffness, tendon jerks, clonus, and pain (Rizzo et al., 2004, Murillo et al., 2011, Sommerfeld et al., 2012). These symptoms limit patients' ability to move and perform functional activities, which in turn reduces quality of life (Murillo et al., 2011). Likewise, in a population of MS patients, severity of spasticity predicted low scores on quality of life measures, demonstrating the importance of developing treatments to combat this symptom (Rizzo et al., 2004).

There are a variety of treatments available for different manifestations of hypertonia. Physical therapy is recommended for treatment of spasticity (Sommerfeld et al., 2012). Mobilization and passive stretch after upper motor neuron damage reduce and may even prevent spasticity (Trompetto et al., 2014). For example, passive movements over 4 weeks reduced spasticity in individuals with SCI (Chang et al., 2013). Additionally, walking is an effective treatment, with one study finding that 4 weeks of body-weight-supported treadmill walking reduced flexor muscle spasms and clonus, increasing mobility and quality of life in individuals with chronic SCI and spasticity (Adams and Hicks, 2011). Muscle vibration is another intervention that has been shown to reduce spinal excitability and spasticity (Murillo et al., 2011). Generally, treatment starts out with physical therapy, which is the least invasive, and is sometimes combined with other treatments, such as oral medications, injections, implants, and surgery (Adams and Hicks, 2005, Sommerfeld et al., 2012).

Anti-spastic medications produce mixed results depending on the individual, and their efficacy is not well-studied (Rizzo et al., 2004). For example, oral intake of baclofen, an agonist for gamma-aminobutyric acid (GABA) B receptors, inhibits spinal reflexes, thereby

reducing spasticity, but it has adverse side effects for stroke and MS patients, including fatigue, muscle weakness, and cognitive difficulties (Sommerfeld et al., 2012). More treatments and physical therapy regimens should be studied to determine if there are alternatives to pharmacological treatments that can alleviate spasticity. Management of spasticity could be improved by evidence-based physical therapy, reducing or eliminating the need for medication and the associated side effects. Better spasticity treatment would benefit a vast and diverse population of people with neurological dysfunction and spasticity.

The Stretch Reflex and the Hoffman (H) Reflex

A good understanding of the stretch reflex pathway is required to understand spasticity. The stretch reflex is elicited when a muscle is stretched, activating muscle spindles and Ia-afferent fibers, which synapse monosynaptically onto α-motoneurons that innervate the same muscle. The resulting muscle contraction opposes further stretch (Trompetto et al., 2014). In healthy individuals, the stretch reflex is only elicited when a joint is moved at a velocity above 175° per second. On the other hand, hemiparetic patients with spasticity experience a stretch reflex when displacement velocity is as low as 35° per second. Additionally, activity in the stretched muscle persists for the duration of the displacement, which is not seen in normal subjects (Thilmann et al., 1991). Even at rest, the stretched muscle is still active (Trompetto et al., 2014). Notably, spastic muscles are more active when the stretch occurs at a faster rate, demonstrating the exaggeration of the stretch reflex and the velocity-dependent nature of its effect (Thilmann et al., 1991).

Upper motor neurons control motor activity through both direct and indirect pathways (Purves et al., 2001). It is thought that damage to one of the indirect pathways,

the dorsal reticulospinal tract, is implicated in increasing the tonic stretch reflex in spasticity (Sheean, 2002). The reticulospinal tract is composed of upper motor neurons in the reticular formation of the brainstem that stabilize posture and coordinate muscle movements by activating or inhibiting interneurons in the spinal cord. Mainly, upper motor neurons provide feed-forward, or anticipatory, muscle activation in order to prepare the body as posture shifts and movement continues (Purves et al., 2001). The dorsal reticulospinal tract specifically inhibits the presynaptic Ia-afferents, and if this descending pathway is damaged, the stretch reflex becomes disinhibited (Sheean, 2002).

In addition to the influence of upper motor neurons, other spinal pathways modulate the Ia-afferent/α-motoneuron synapse. Depending on the disease and type of CNS lesion, many pathways can become abnormal and contribute to spasticity. It was only recently discovered that abnormality in an inhibitory presynaptic mechanism, post-activation depression, is strongly correlated with severity of hypertonia. Post-activation depression is caused by repeated activation of the Ia-afferents, thereby reducing neurotransmitter availability (Lamy et al., 2009). Without normal post-activation depression, neurotransmitters are more frequently released from the Ia-afferent terminals, causing more α-motoneuron excitation.

The Hoffman (H) reflex is often used to study the stretch reflex neural pathway. An H-reflex is elicited by electrical stimulation of a peripheral nerve that includes both Ia-afferent axons that emanate from muscle spindles and α-motoneuron axons that contract the same muscle (Zehr, 2002). The main difference between a stretch reflex and an H-reflex is that the H-reflex is triggered without the activation of muscle spindles, making it a measure of neurotransmission at the Ia afferent/α-motoneuron synapses (Palmieri et al.,

2004). Notably, the H-reflex is also not a direct measure of the excitability of the α-motoneuron pool. Instead, H-reflex size is determined by presynaptic and postsynaptic influences (Knikou, 2008).

The H-reflex is expressed as the ratio of the largest H-reflex (H_{max}) to the largest M-wave (M_{max})(Figure 1C). The M-wave is the motor response resulting from direct electrical stimulation of α-motoneuron axons in the peripheral nerve. The M_{max} is the maximum motor unit recruitment, and it is used to standardize H-reflexes across subjects. The muscle contractions elicited by both the M-wave and H-reflex are recorded by electromyographic (EMG) activity from surface electrodes placed on the muscle of interest (Figure 1A). The M-wave has the shorter latency because the stimulus has a shorter distance to travel before reaching the muscle. The H-reflex is the motor response elicited by the stretch reflex arc. To find the H_{max} and M_{max}, the peripheral nerve is stimulated with a range of stimuli from small to large until the largest amplitudes are found for the M-wave and H-reflex (Figure 1B). The Ia-afferent axons are recruited before the smaller diameter α-motoneuron axons, so it is normal to observe an H-reflex without an M-wave. At larger stimulus intensities, H-reflexes will shrink while M-waves grow because antidromic impulses in the α-motoneurons oppose the action potentials from the reflex arc (Zehr, 2002).

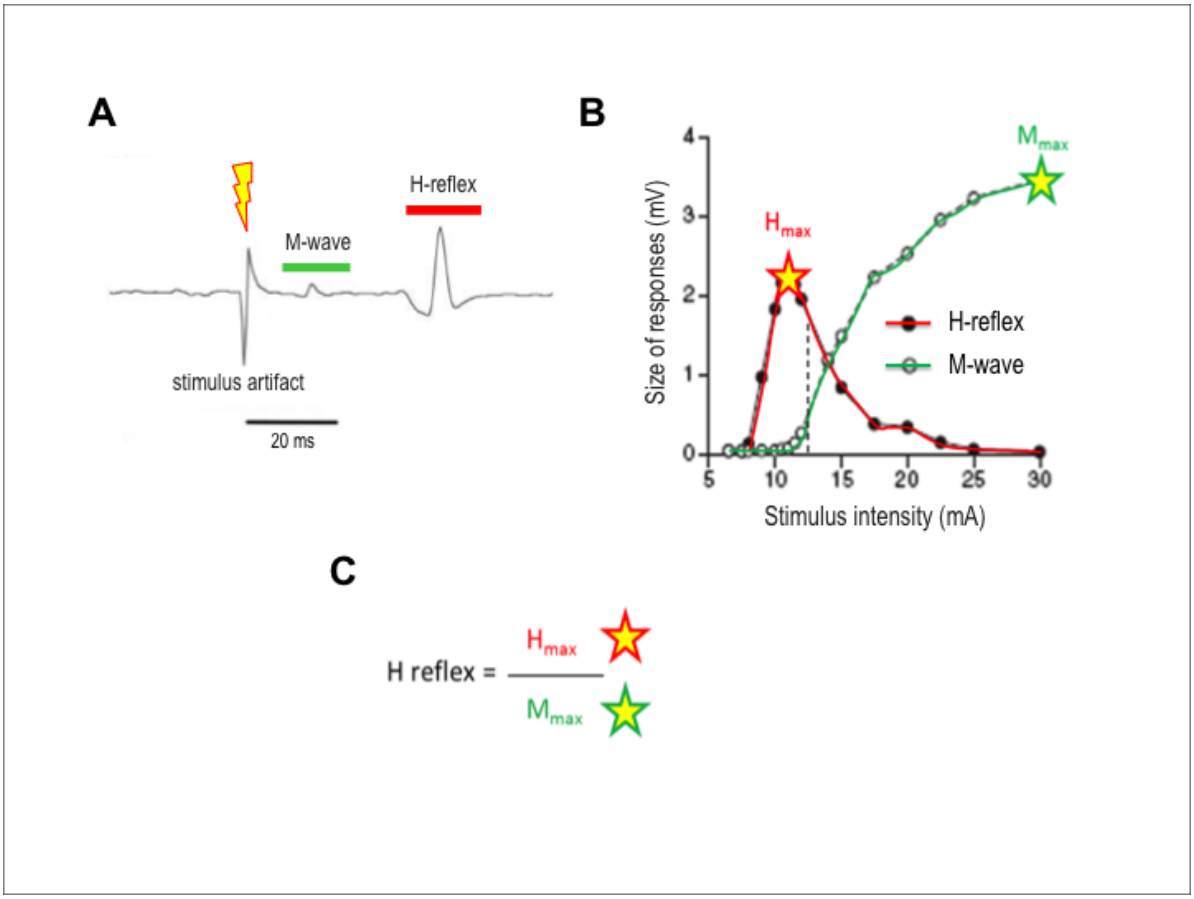


Figure 1. Measuring the H-reflex. A) EMG activity. M-wave and H-reflex sizes are found by measuring the peak-to-peak amplitudes. B) A typical H-reflex and M-wave recruitment curve. C) The H-reflex is characterized as the ratio of H_{max} to M_{max} (adapted from Zehr, 2002).

The H-reflex has been studied in a variety of muscles. The soleus (Sol) is the most commonly studied lower limb muscle because H-reflexes are more easily elicited in the Sol than in other muscles (Tucker et al., 2005). The most commonly studied muscle of the upper limbs is the flexor carpi radialis (Zehr, 2002). Few studies have investigated tibialis anterior (TA), which is the antagonist of the Sol, because the TA H-reflex amplitude is small compared to the Sol H-reflex and is sometimes difficult to elicit. For example, Brooke et al.

(1997) found average TA H-reflexes between 10% and 13.5% M_{max}. On the other hand, Sol H-reflexes can be as large as 80% M_{max} (Misiaszek et al., 1995).

Studying H-reflexes is relevant to the study of spasticity because hypertonia correlates with elevated H-reflexes (Dimitrijevic and Nathan, 1967, Levin and Hui-Chan, 1993, Morita et al., 2001). Further, a reduction in H-reflexes induced by acute leg cycling has been found to correspond with reduced hypertonia (Motl et al., 2006). Non-pharmacological interventions that elicit H-reflex depression are needed to help researchers understand the neural underpinnings of spasticity, and to directly reduce symptoms while maintaining or improving fitness and avoiding side effects of medications.

H-Reflex Modulation

As stated in the previous section, the monosynaptic pathway of the stretch reflex is modulated by a variety of spinal inputs both presynaptically and postsynaptically (Knikou, 2008). These inputs include cortical control and afferent feedback from receptors in activated muscles, such as muscle spindles and Golgi tendon organs (Zehr, 2002). Presynaptic modulation occurs through inhibitory interneurons that synapse onto Ia-afferent presynaptic terminals and reduce neurotransmitter release. Postsynaptic modulation occurs through both inhibitory and excitatory inputs that determine the likelihood that α-motoneurons will fire an action potential due to neurotransmitters released from the Ia-afferent terminals (Tucker et al., 2005).

Several pathways and patterns of muscle activation are thought to increase or decrease presynaptic inhibition of the Ia-afferent terminals. As stated previously, the dorsal reticulospinal tract and post-activation depression both mediate presynaptic inhibition (Purves et al., 2001, Sheean, 2002, Lamy et al., 2009). Additionally, posture affects the

amount of presynaptic inhibition. For example, standing causes more presynaptic inhibition compared with a prone position (Zehr, 2002). On the other hand, the Jendrassik maneuver, which is the contraction of a muscle or muscles not directly involved in the H-reflex (such as the forearm extensor and the muscles that control jaw clenching) decreases presynaptic inhibition and therefore increases the H-reflex response in the lower limbs (Dowman and Wolpaw, 1988, Zehr and Stein, 1999). Femoral nerve stimulation, which activates the leg extensors, also reduces presynaptic inhibition and facilitates the Sol H-reflex (Zehr, 2002).

Other spinal pathways influence the Ia afferent/α-motoneuron synapse postsynaptically. For example, reciprocal inhibition is a disynaptic pathway mediated by Ia inhibitory interneurons that inhibit antagonist α-motoneurons when the agonist contracts (Zehr, 2002). For example, either vibrating the TA or stimulating the common peroneal nerve that innervates the TA attenuates the Sol H-reflex (Eccles et al., 1962, Iles and Roberts, 1987). Renshaw cells also mediate postsynaptic modulation through a negative feedback process called recurrent inhibition and play a significant role in motor control (Knikou, 2008). These inhibitory interneurons located in the ventral horn of the spinal cord are activated by collaterals projecting from α-motoneuron axons, and they postsynaptically inhibit the α-motoneurons that project to the same or synergistic muscles (Renshaw, 1946). Generally, recurrent inhibition is engaged when a new muscle synergy pattern is required for a complex movement and when equilibrium is challenged (Knikou, 2008).

Much research has been performed to determine how various interventions influence neurotransmission at the Ia-afferent/α-motoneuron synapse by measuring the H-reflex, as well as other pathways that are thought to influence the H-reflex, during, or

before and after movement. For example, Sol H-reflexes are large during the stance phase of walking and during down-stroke pedaling on a stationary bike, when the Sol is active, and reduced or nonexistent during the swing phase of walking and during upstroke pedaling, when the Sol is silent (Capaday and Stein, 1986, Boorman et al., 1992). Other spinal pathways, such as recurrent inhibition, are also activated rhythmically during locomotion to regulate movement (Pratt and Jordan, 1987).

Cross-sectional studies have demonstrated that the type of activity an individual regularly performs predicts the neural adaptations in the spinal cord. According to Wolpaw and Tennissen (2001), "the spinal cord plasticity that underlies training-induced functional improvement clearly depends on the pattern of afferent, efferent, and interneuronal activity that occurs during training." The authors call this phenomenon "activity-dependent spinal cord plasticity" (Wolpaw and Tennissen, 2001). Various athletes have been studied to determine the correlation between repeated and specified training on spinal excitability compared with other active and non-active individuals. Athletes who regularly performed explosive training have smaller Sol H-reflexes than untrained participants (Casabona et al., 1990). On the other hand, endurance trained athletes have larger Sol H-reflexes compared to untrained and explosive-trained athletes (Maffiuletti et al., 2001). Additionally, professional ballet dancers have depressed H-reflexes compared with active individuals (Nielsen et al., 1993). Training also affects pre- and postsynaptic mechanisms that regulate stretch reflex excitability. For example, ballet dancers have less reciprocal inhibition than other active individuals due to prolonged co-activation of the Sol and TA, likely contributing to Sol H-reflex depression (Nielsen et al., 1993). In addition, endurance-trained athletes have greater post-activation depression and less recurrent inhibition

compared to power-trained and untrained individuals (Earles et al., 2002). These studies demonstrate that physical activity and training are correlated with adaptations of the stretch reflex pathway and the pathways that influence the stretch reflex.

Several experiments have also measured H-reflexes before and after an activity or intervention. For example, Thompson et al. (2006) found that Sol H-reflexes were reduced by 10% after 30 minutes of walking on a level treadmill, lasting until 30 minutes after the exercise. Operant conditioning of the H-reflex using visual feedback also reduced Sol H-reflexes and improved walking speed in people with incomplete SCI (Thompson et al., 2013). Another study found that H-reflexes and stretch reflexes were reduced during and at least up to 5 minutes after whole body vibration (Ritzmann et al., 2013), as well as after prolonged muscle vibration (Shinohara, 2005). A final example of post-intervention H-reflex depression is a study that found Sol H-reflexes were attenuated 10 minutes after cycling on an ergometer (Motl and Dishman, 2003). These studies demonstrate that a variety of interventions can reduce spinal excitability.

Downslope Walking (DSW) and H-Reflex Depression

Locomotion is controlled mainly by the spinal cord (Dietz, 1992, Dimitrijevic et al., 1998). Many interconnected spinal neurons come together to form a locomotor pattern generator (LPG) that is activated by supraspinal commands through the brainstem and thalamus and is continually adjusted by the spinal cord using afferent and efferent feedback (Wolpaw and Tennissen, 2001). The LPG is capable of maintaining a normal walking pattern without supraspinal control, which is evident in cats whose spinal cords have been transected (Barbeau and Rossignol, 1987). Additionally, humans with SCI can recover and improve locomotion by treadmill walking (Adams and Hicks, 2011). Walking

has other benefits and can significantly improve strength, endurance, coordination, and quality of life in a neurologically damaged population (Wolpaw and Tennissen, 2001, Adams and Hicks, 2011).

Recent studies have investigated how walking uphill or downhill affects spinal excitability. Bulbulian and Bowles (2008) found that running at an intensity of 50% of maximal oxygen uptake on both a level and -10% grade slope for 20 minutes reduced H_{max}/M_{max} ratios, with the downslope condition resulting in a larger reduction. Our lab recently found that Sol H-reflexes were depressed after 20 minutes of level walking (LW) and downslope walking (DSW) at a -15% slope, and the effect was 5 times larger for DSW (Sabatier et al., 2015). A unique feature of DSW is a bias towards more eccentric contractions in lower extremity muscles. Eccentric contractions alone can cause H-reflex depression. For example, lengthening of the Sol while it contracts (i.e. eccentric muscle contraction) depresses Sol H-reflexes as opposed to shortening of the muscle (i.e. concentric muscle contraction) (Nordlund et al., 2002). These findings support the idea that eccentric-biased locomotion promotes H-reflex depression.

DSW has a variety of benefits in addition to attenuating Sol H-reflexes (Sabatier et al., 2015). For example, DSW is more effective than upslope walking at improving gait speed in patients with stroke (Carda et al., 2013). DSW also reduces trunk flexion (Leroux et al., 2002). Lastly, it was discovered that DSW for 4 weeks is more effective than conventional therapy at improving gait, muscle strength of knee extensors, and maintaining thoracic posture in Parkinson's Disease (Yang et al., 2010). These examples demonstrate that DSW can benefit a variety of neurologically damaged populations.

Importantly, DSW can be performed with weight support if needed and is a light activity without much cardiovascular or perceived strain (Sabatier et al., 2015).

Our finding that DSW causes a much larger decrease in Sol H-reflexes compared to LW suggests that there could be a dose-response effect of slope on H-reflexes (Sabatier et al., 2015). Dose-response, or dose-dependent, effects are typical for exercise, but unknown for the effect of DSW on spinal excitability. In fact, no other studies have established a dose-response effect of any exercise on H-reflexes. The effect of medications on H-reflexes, on the other hand, has been studied. For example, a dose-response effect has been established for intrathecal baclofen on both the H-reflex and spasticity (Stokic et al., 2006). In addition, a dose-response effect was found for intramuscular botulinum toxin type A on attenuating muscle tone in stroke patients who have spasticity in their elbow, wrist, and fingers (Childers et al., 2004). These results suggest that a dose-response effect of DSW on H-reflexes is possible.

While Sol H-reflex depression has been documented for DSW, it is unknown if this effect is generalizable to the TA (Sabatier et al., 2015). Few studies have evaluated the effect of exercise or movement on the TA H-reflex because it is difficult to elicit. However, we believe that there may be an effect because Brooke et al. (1997) found that TA H-reflexes were attenuated about 18%, which amounted to a reduction of 2.0% TA $M_{\max}$, during passive cycling motion of the lower limb. TA H-reflex depression after DSW would suggest the effect of DSW on spinal excitability is not isolated to the Sol, and that H-reflex depression after DSW could be a widespread neural adaptation, irrespective of the skeletal muscle's functional role in movement.

The neural mechanisms that explain acute H-reflex depression following DSW are not well understood, warranting further research. The neural complexity of the eccentric-biased exercise, which induces an up- or down-regulation of neural pathways that modulate the Ia afferent/alpha-motoneuron synapses, is likely a component that causes H-reflex depression. Eccentric muscle contractions during DSW might increase muscle spindle activity, causing Ia-afferent feedback to be down-regulated at the synapse (Sabatier et al., 2015), or promote more supraspinal control since cortical activity is increased during eccentric contractions (Fang et al., 2001, 2004). Cortical activity also influences spinal excitability in other ways, such as modulating postsynaptic inhibition by activating or inhibiting Renshaw cells (Nielsen and Pierrot-Deseilligny, 1996). Our lab has evaluated two presynaptic mechanisms that could be involved in reducing Sol H-reflexes. We have found that there was no change in post-activation depression following DSW (Sabatier et al., 2015), but there was a depression in H-reflex augmentation with the Jendrassik Maneuver following 20 minutes of DSW at a -15% slope (Moise et al., 2015), suggesting an increase in supraspinal presynaptic inhibition following DSW.

We propose that recurrent inhibition may also mediate H-reflex depression following DSW through postsynaptic inhibition. Collaterals from large diameter α-motoneurons activate Renshaw cells more readily, inhibiting small diameter α-motoneurons at a faster rate (Pompeiano, 1984). There is some evidence that eccentric-biased exercise recruits faster motor units (Nardone et al., 1989). Therefore, selective recruitment of fast, large diameter alpha-motoneurons during DSW may result in more recurrent inhibition. Additionally, Renshaw cell activity increases during co-contraction of antagonist muscles and when a new muscle synergy pattern is required for a complex

movement when equilibrium is challenged (Nielsen and Pierrot-Deseilligny, 1996, Knikou, 2008). DSW also involves co-contraction of the Sol and TA (Lay et al., 2007) and challenges balance, therefore potentially increasing Renshaw cell activity to mediate spinal plasticity.

The current study's goal is to determine if DSW affects spinal excitability in a dose-dependent manner by varying time (10 minutes vs. 20 minutes) and slope (-15% decline vs. -25% decline) of DSW. Another goal is to determine if the effect of DSW on the H-reflex pathway is generalizable to other muscles by also evaluating TA H-reflexes before and after DSW. The last major goal of this study is to determine if Sol recurrent inhibition is affected by DSW.

Hypotheses

H-reflex depression after DSW will be greater when the duration is 20 minutes than when the duration is 10 minutes. H-reflex depression after DSW will be greater when the decline is -25% than when the decline is -15%. DSW will increase Sol recurrent inhibition

Methods

Participants

Twelve healthy, neurologically intact adults (6 men and 6 women) between ages 22 and 30 were tested four or five times in a period of two weeks. Participants had the following characteristics (mean ± SD): age: 24.8 ± 2.0, height: 170.8 ± 9.3 cm, mass: 64.3 ± 12.4 kg, BMI: 21.9 ± 3.3 kg/m^2. Participants were recruited from Emory University's campus and completed an informed consent approved by the Institutional Review Board at Emory University before participation.

Design

The study used a within-subject and repeated measures design. The dominant leg was tested for each participant at the same time of day in order to avoid diurnal effects on H-reflex size (Wolpaw and Seegal, 1982, Lagerquist et al., 2005). There were four DSW combinations: 10 minutes at -15%, 20 minutes at -15%, 10 minutes at -25%, 20 minutes at -25%. In order to control for a training effect over the course of the study, the first half of the participants started at the -15% decline and the second half started at the -25% decline. Participants walked the 10-minute duration first for a given slope to minimize the potential for delayed onset muscle soreness (DOMS), though previous research has found that muscle soreness does not affect spinal excitability (Behrens et al., 2012, Moise et al., 2015). One or two days separated each session, and the participants completed the study within two weeks. Eight participants also completed a LW session for 20 minutes to act as a control group.

The first session lasted between 3 and 3.5 hours, and the following sessions lasted between 2.5 and 3 hours. The first session was the longest because the laboratory technicians had to probe for the tibial nerve and the common peroneal nerve. After electrode placement, the participants were seated in a semi-reclined position with the hip at 120° and knee at 30°. The lower limbs were placed into braces and secured together with a strap to prevent external rotation or abduction. Next, maximum Sol and TA EMG were measured during isometric contractions and then baseline excitability measurements were collected in this order: Sol H-reflex and M-wave (H-M) recruitment curve, Sol recurrent inhibition, and TA H-M recruitment curve. Afterwards, the participants walked

on the treadmill, rested for five minutes, and dependent measurements were collected again.

Walking Procedure

All participants walked downslope on a Sole Fitness F85 Folding Treadmill (Niagra Falls, ON) at 4.0 km/h (2.5 mph) for each walking condition. Spinal excitability measures and Sol recurrent inhibition were recorded before and after walking. Prior to walking, heart rate (HR) was measured by palpating the radial artery to record a 10-second count. During the third minute of every five-minute walking segment, or epoch, HR was measured and ratings of perceived exertion (RPE) were collected using the Borg scale, with 6 being "very, very light" to 19 being "very, very hard" (Borg, 1978). Participants were seated immediately after walking, and HR was measured after 5 minutes.

Soleus H-Reflexes

At the beginning of each session, two bipolar surface electrodes (EL503; Biopac Systems Inc.) were placed on the Sol, 2 cm apart and along the posterior lateral part of the muscle, 2 cm inferior to the lateral gastrocnemius, to record electromyographic (EMG) activity. An additional electrode was placed on the lateral malleolus to ground, and an anode (square, 5 cm) was also placed above the patella (Basmajian and Blumenstein, 1989). At the beginning of the first session with the participant in a prone position, the location of the tibial nerve in the popliteal fossa was found by using a pen electrode (Model G.MPPE, Digitimer, Hertfordshire, AL7 3BE, England). The optimal placement of a monopolar electrode (round, 2.5 cm) was determined to be the location that elicited consistent Sol H-reflexes without an M-wave and plantarflexion without eversion or inversion. Both the cathode and anode were self-adhering carbon rubber TENS/ NMES

electrodes (Medical Products Online, Danbury, CT). All electrodes were outlined after each session with a permanent marker to ensure consistency in stimulation and recording sites throughout the study. EMG signals were band-pass filtered (5–1000 Hz) and amplified by 2000 (Biopac Systems Inc, BN-EMG2). The size of the H-reflex and M-waves were measured as the peak-to-peak amplitudes of the Sol EMG (mV).

Sol H-reflexes were evoked by stimulating the tibial nerve through the monopolar electrode with a 1-ms rectangular pulse of constant current using an electrical stimulator (Biopac STMISOLA; STIMSOC) while the participant was seated in the semi-reclined position. To obtain the Sol H-M recruitment curves, the tibial nerve was stimulated with sixty pulses of increasing intensity every 5-8 seconds until the largest H-reflex (H_{max}) and the largest M-wave (M_{max}) were found. The participant also performed isometric plantarflexion against the leg brace and used biofeedback to maintained 20% of maximum Sol EMG activity in order to control α-motoneuron excitability (Zehr, 2002). Ankle joint angle and voluntary contraction were also controlled because these factors impact M_{max} and H_{max} size (Frigon et al., 2007). The H-reflex was expressed as the ratio of H_{max} to M_{max}.

Tibialis Anterior H-Reflexes

TA H-reflexes were found using a similar procedure described above for the Sol, except that a bipolar stimulating electrode was placed on the common peroneal nerve, which is located above the fibular head on the lateral leg. Two bipolar surface electrodes were placed on the muscle belly of the TA, 2 cm apart (Basmajian and Blumenstein, 1989). Participants provided 20% of maximum TA EMG background activity using biofeedback during data collection.

Recurrent Inhibition

Sol recurrent inhibition was measured by collecting Sol H-reflexes every 6 seconds for 30 repetitions, alternating between two stimulus intensities. The participant rested and provided no Sol background activity. A low intensity stimulus was used first, eliciting the unconditioned H-reflex (H1) that was maintained at 10% of M_{max}. H1 must remain constant because recurrent inhibition is dependent on the size of H1 (Pierrot-Deseilligny et al., 1976). The second stimulus size was the same low intensity stimulus along with a supramaximal stimulus 10 ms later, which elicited the conditioned H-reflex (H'). The intensity of the supramaximal stimulus was 1.2 x motor threshold. The extent to which H' is smaller than H1 represents recurrent inhibition. The percent difference between H1 and H' was calculated using the following equation: (H' – H1)/H1*100. Higher percent depression denotes more recurrent inhibition.

Statistical Analysis

The effects of the independent variables (slope and duration) on the dependent variables (H_{max}/M_{max} ratio, and percent depression) were evaluated. The within-subject repeated measures design was modeled using a generalized linear model with day as a fixed effect, pre-post as a fixed effect, and random effects for subject nested within time point. The normality assumption was checked visually via Q-Q plots, and standardized residuals were plotted versus fitted values to evaluate the independence assumption of residuals. If the interaction term for the model was significant, the least significant difference pair-wise test was used to evaluate comparisons of interest. Interaction terms are only referenced in the results section if statistically significant. Statistica data analysis

software system (version 12.7, StatSoft, Inc., 2013) was used for all statistical analyses and the significance level was set at $P \leq 0.05$.

Results

Heart Rate, Perceived Exertion, and Soreness

During DSW, heart rate (HR) and ratings of perceived exertion (RPE) were measured during the third minute of each epoch, and HR was also measured before and after walking (Figure 2). The main effects for epoch ($P < 0.001$) and slope ($P < 0.001$) were significant for HR. Paired t-tests were used to compare HR between -15% and -25% slopes at each epoch, and between the same slope at different epochs, revealing increased HR when walking at -25% slope compared to -15% slope, irrespective of DSW duration ($P \leq 0.05$), and increased HR during walking at -25% slope during the 3rd and 4th epoch compared to the 1st and 2nd epoch ($P \leq 0.05$). There was no significant change in HR across walking durations and doses at -15%.

For RPE the main effects for epoch ($P < 0.001$) and dose ($P < 0.001$) were significant. Paired t-tests were used to compare RPE between -15% and -25% slopes at each epoch, and between the same slope at different epochs, revealing increased RPE when walking at -25% slope compared to -15% slope ($P \leq 0.05$), and increased RPE during walking at -25% slope during the 3rd and 4th epoch compared to the 1st and 2nd epoch ($P \leq 0.05$). There was no significant change in RPE for across walking durations and doses at -15%.

Additionally, participants who started the study walking on the -15% slope did not report any lower extremity muscle soreness. On the other hand, participants who started with the -25% slope reported soreness primarily in the TA, triceps surae, and quadriceps.

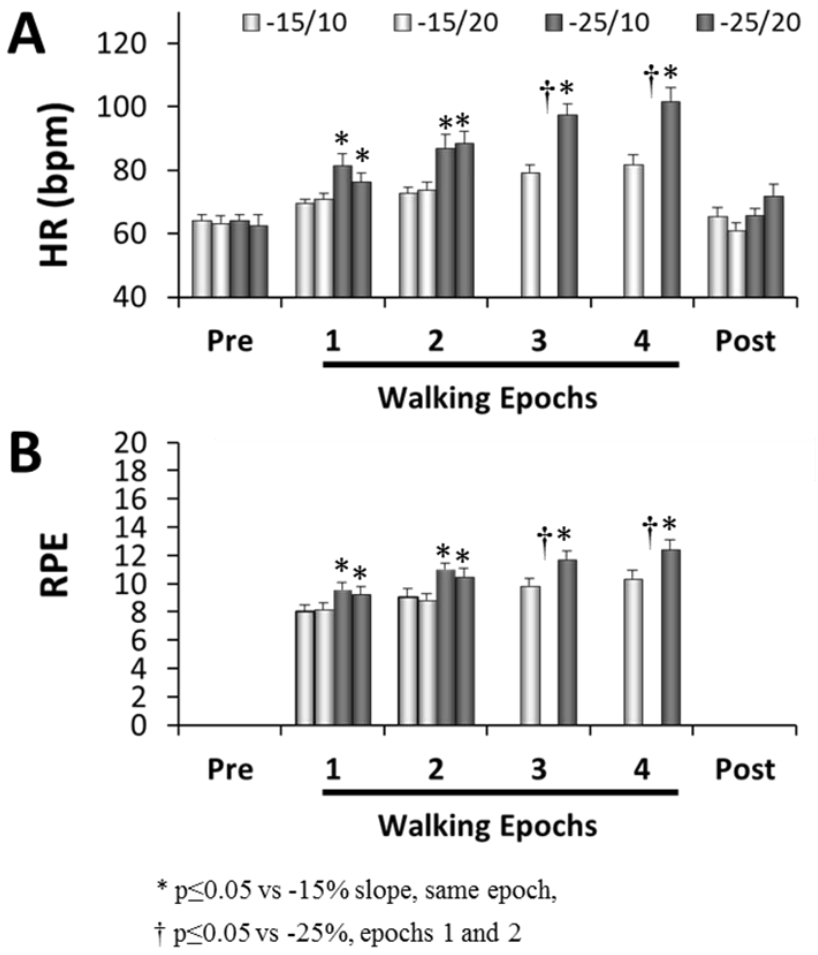


Figure 2. Heart rate and ratings of perceived exertion during DSW. Average heart rate (HR) and ratings of perceived exertion (RPE) during DSW at -25% was significantly elevated compared to -15% in each epoch ($P \leq 0.05$). Additionally, HR and RPE during DSW at -25% were higher during the 3rd and 4th epoch compared to the 1st and 2nd epoch ($P \leq 0.05$).

Soleus and TA H_{max}/M_{max} Ratios

In Figure 3, representative Sol and TA H-reflex and M-response curves are shown from a participant before and after DSW for 20 minutes at -25%. Table 1 includes quantitative values for Sol H_{max}, M_{max}, H_{max}/M_{max} ratios, and percent depression, and Figure 4A and 4B illustrates Sol and TA H_{max}/M_{max} ratios before and after each DSW condition,

including 20 minutes of LW. Baseline Sol H_{max}/M_{max} was moderately reliable across days (ICC= 0.75). Neither day (P = 0.18) nor the interaction term (P = 0.30) was significant, but pre vs. post was significant (P < 0.001). Percent depression of Sol H_{max}/M_{max} ratios was also evaluated (Figure 4C), and there was a significant main effect for Sol H_{max}/M_{max} percent depression (P = 0.01). Post hoc analysis revealed that percent depression after all DSW doses except 10 minutes at -15% (P = 0.61) were significantly different from LW ($P \leq 0.02$). Additionally, percent depression of Sol H_{max}/M_{max} ratios after DSW for 20 minutes at -25% was significantly different from DSW for 10 minutes at -15% (P = 0.01). Thus, DSW at all but the smallest dose resulted in more Sol H_{max}/M_{max} depression than LW for 20 minutes, and differential effects of slope and duration on Sol H-reflex depression are only apparent when comparing the smallest to the largest dose of DSW.

Baseline TA H_{max}/M_{max} ratios were moderately reliable across days (ICC=0.61). Neither day (P = 0.55), pre vs. post (P = 0.10), nor the interaction term (P = 0.84) was significant. Additionally, the main effect of percent depression of TA H_{max}/M_{max} ratios was not significant (Figure 4D). Therefore, DSW and LW had no effect on TA H_{max}/M_{max} ratios.

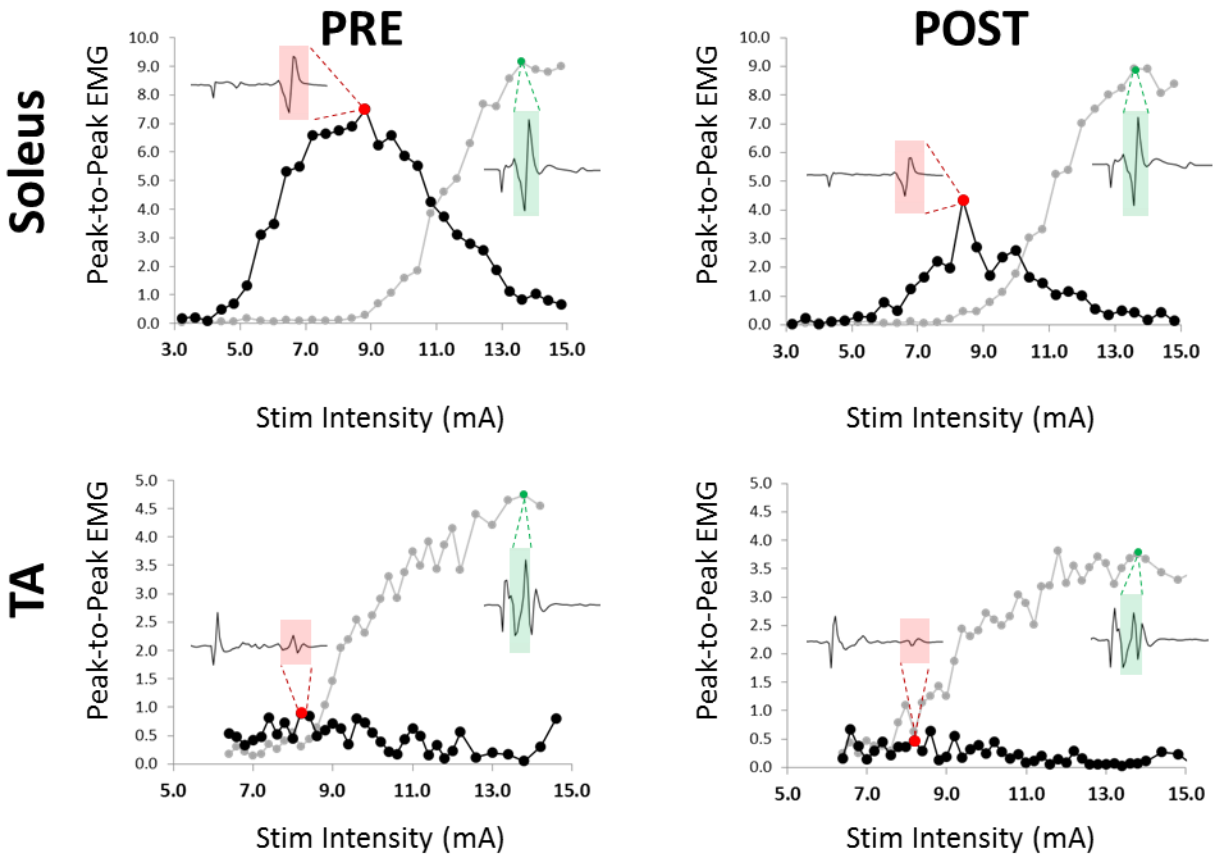


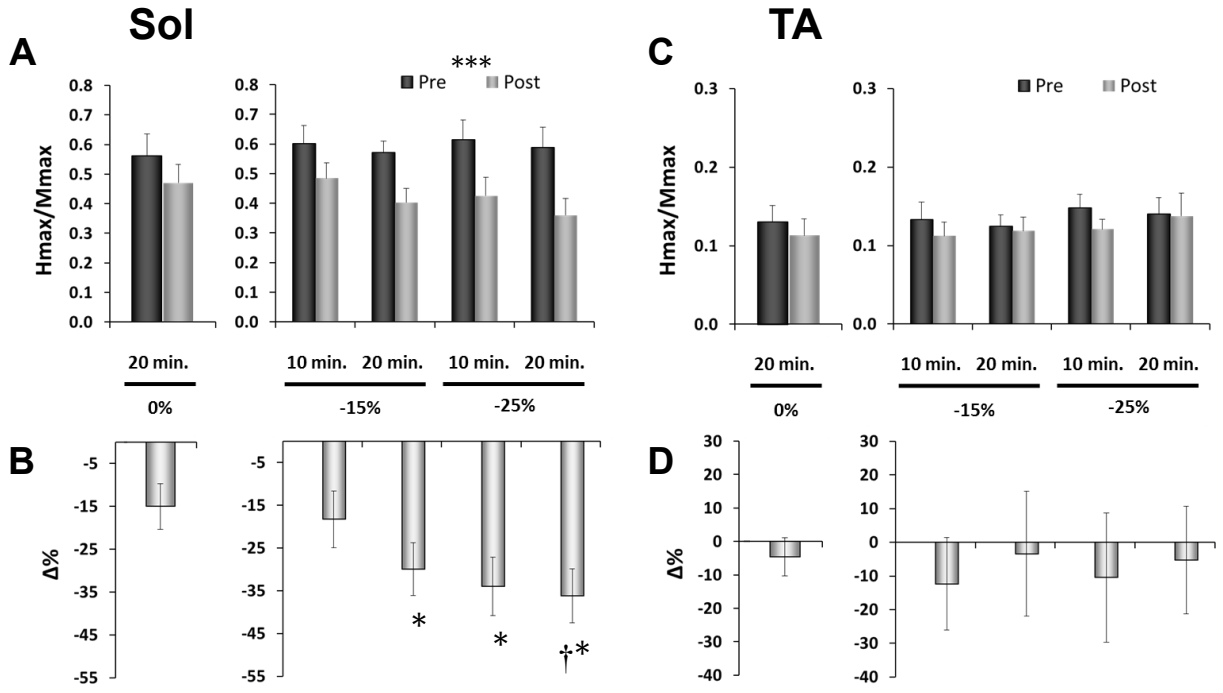
Figure 3. Representative Sol and TA H-M recruitment curves and raw EMG collected before and after DSW. The black dots represent the H-reflex and the grey dots represent the M-wave. Stimuli were administered as constant-current (mA). The peak-to-peak amplitudes from the EMG (mV) determined the sizes of the H-reflex and M-wave. The raw EMG signals are approximate representations of the Sol and TA H_{max} and M_{max}. This data is from a participant who walked for 20 minutes at a -25% slope.

Table 1. Maximum Sol H-reflexes and M-responses (peak-to-peak amplitude, mV), H_{max}/M_{max} ratios, and percent depression.

	0%	-15%		-25%	
	20 mins	10 mins	20 mins	10 mins	20 mins
H_{max}					
Pre	4.6(1.8)	4.5(2.5)	4.3(1.8)	4.7(2.2)	4.2(2.3)
Post	3.8(1.6)	3.3(1.8)	*2.8(1.3)	*3.0(1.9)	*2.3(1.4)
M_{max}					
Pre	8.0(1.2)	7.1(2.3)	7.3(2.4)	7.3(1.8)	7.1(1.8)
Post	8.0(0.9)	6.4(2.2)	6.9(2.1)	6.7(2.3)	6.2(1.8)
H_{max}/M_{max}					
Pre	0.6(0.2)	0.6(0.2)	0.6(0.1)	0.6(0.2)	0.6(0.2)
Post	0.5(0.2)	0.5(0.2)	*0.4(0.2)	*0.4(0.2)	*0.4(0.2)
% dep.	15(15%)	18(23%)	#30(21%)	#34(23%)	†#36(22%)

Values are reported as mean(SD).

* $P \leq 0.05$ vs Pre
# $P \leq 0.02$ vs LW
† $P = 0.01$ vs. 10 min. at -15%



*** $P \leq 0.001$, Sol Pre vs. Post
* $P \leq 0.02$ vs. LW
† $P = 0.01$ vs. 10 min. at -15%

Figure 4. Sol and TA H_{max}/M_{max} ratios before and after downslope and level walking and percent depression. (A) Sol H_{max}/M_{max}, mean + SE, P < 0.001. The main effect of pre vs. post is significant. (B) Sol H_{max}/M_{max} percent depression, mean ± SE, $P \leq 0.02$ vs. LW, $P = 0.01$ vs. 10 minutes at -15%. Sol H_{max}/M_{max} depression was significantly more negative following all DSW conditions compared to LW, except 10 minutes at -15%. H_{max}/M_{max} depression following 20 minutes at -25% compared to 10 minutes at -15% was also significant. (C&D) There was no significant effect of DSW or LW on TA H_{max}/M_{max} ratios.

Recurrent Inhibition

Figure 5 shows representative recurrent inhibition data from one participant. Recurrent inhibition results before and after DSW are shown in Figure 6. Four of 48 sessions are not included in averages or analysis due to an inability to maintain unconditioned H-reflexes (H1) at 10% of M_{max} (i.e. two testing days for one participant, and one day each for two other participants). Baseline recurrent inhibition was moderately reliable across days (ICC=0.71). Neither day (p=0.42), pre-post (p=0.10), nor the

interaction term (p=0.88) was significant (Figure 6A). The pre-post percent change of recurrent inhibition was also evaluated (Figure 6B), and the main effect of day was not significant (P = 0.37). H1 reflexes, which are used in the denominator when computing recurrent inhibition, were controlled in this study to be 10% of M_{max} (overall average across pre-post and days, 11.4 ± 2.1% of M_{max}, data not shown). For H1, neither day (P = 0.49), pre vs. post (P = 0.07), nor the interaction term (P = 0.81) was significant. Therefore, there were no differences in H1 size that would limit this study's ability to detect statistical changes in recurrent inhibition.

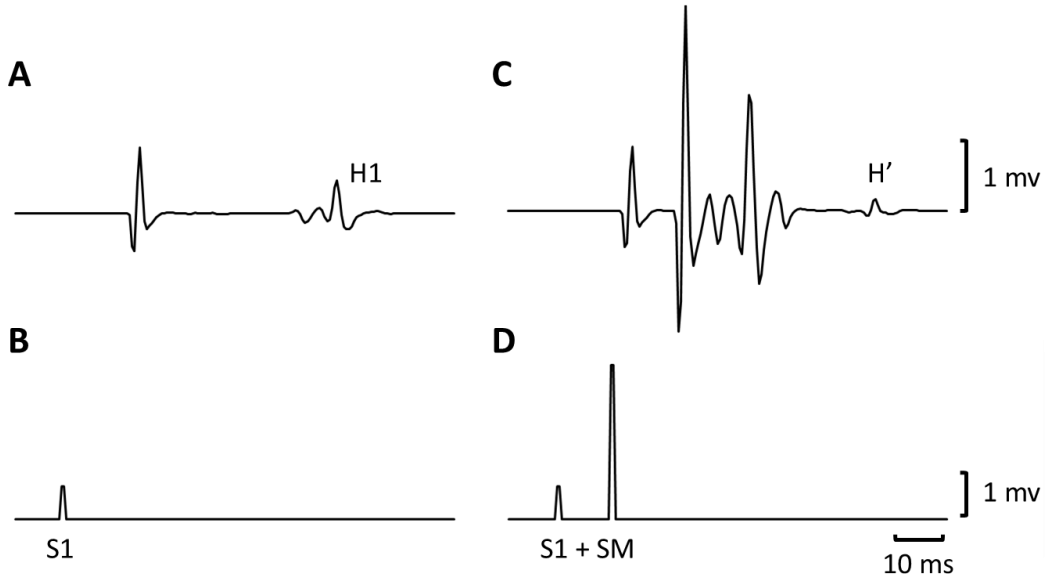


Figure 5. Recurrent inhibition raw data. (A) The unconditioned H-reflex (H1) in the EMG response after a small intensity stimulus (S1), shown in (B). (C) The conditioned H-reflex (H') in the EMG response after S1 + a supramaximal stimulus (SM) 10 ms later, shown in (D). Adapted from Pierrot-Deseilligny et al., 1976.

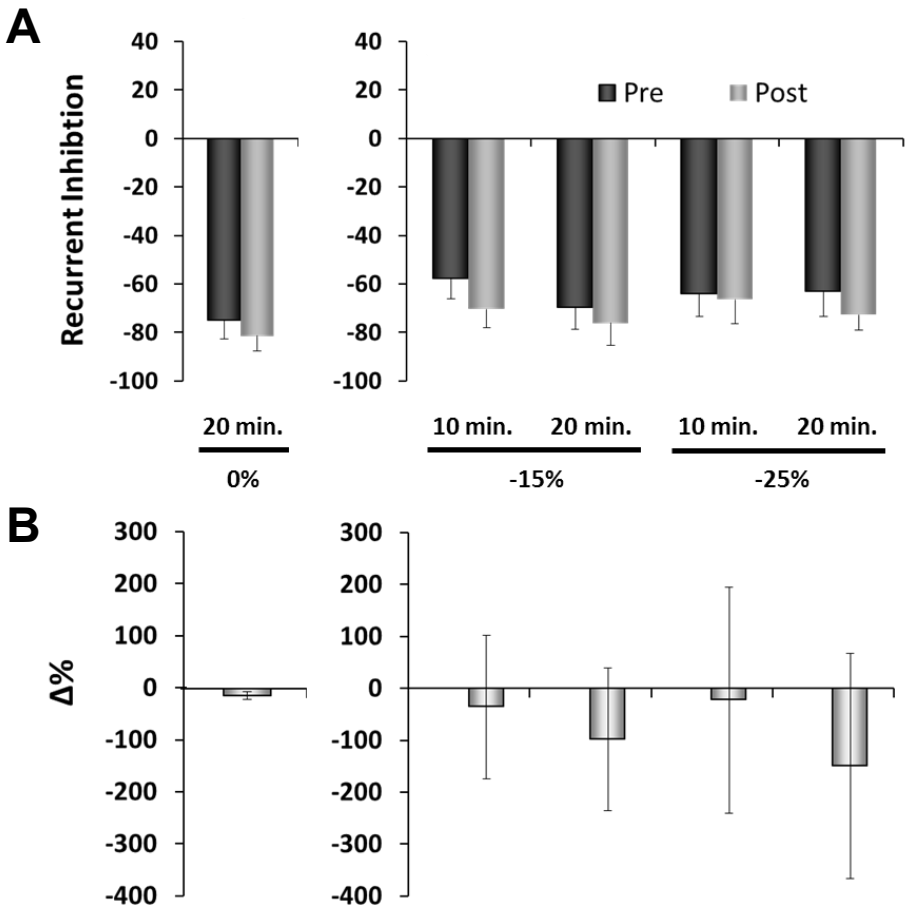


Figure 6. Recurrent inhibition before and after DSW and LW. (A) Recurrent inhibition, mean + SE. There were no significant effects of DSW or LW on recurrent inhibition. There was a trend towards more recurrent inhibition following DSW for some walking conditions. (B) Percent change, mean ± SE. Percent change of recurrent inhibition was more negative following 20 minutes of walking than 10 minutes, regardless of slope.

Discussion

This study is the first to investigate a dose-response effect of exercise on H-reflexes. Previous research found that LW and DSW at -15% for 20 minutes causes Sol H-reflex depression, with the DSW condition causing a much larger reduction (Sabatier et al., 2015). The current study tested the primary hypotheses that H-reflex depression after DSW is greater when the duration of walking is 20 minutes than when the duration is 10 minutes,

and that H-reflex depression after DSW is greater when the decline is -25% than when the decline is -15%. The major finding of this study is a dose-response effect of DSW on Sol H-reflexes, but only when comparing the largest DSW dose (20 minutes at -25% slope) to the smallest DSW dose (10 minutes at -15% slope). This study also found that unlike Sol H-reflexes, TA H-reflexes are not affected by LW or DSW. Therefore, the neural adaptations induced by DSW may not be generalizable across antagonistic muscle pairs. This study expands our knowledge of DSW by demonstrating that the dose, or intensity, of DSW determines the resulting depression of the Sol H-reflex pathway.

Effects of Slope and Duration of Downslope Walking on H-reflexes

Sol H_{max}/M_{max} ratio depression was larger following DSW for all walking conditions compared to LW, except 10 minutes at -15%, which was not significantly different from LW. Therefore, at least 20 minutes of DSW at -15% is required to elicit a larger reduction in Sol H-reflexes than 20 minutes of LW. Acute H-reflex depression has previously been reported for other types of exercise. For example, acute leg-cycling (Motl and Dishman, 2003) and balance training (Trimble and Koceja, 2001) reduces Sol H-reflexes by about 40% and 16%, respectively. Further, increasing the complexity of the exercise augments spinal plasticity. For example, cycling with varying resistance induces more Sol H-reflex depression compared to constant resistance cycling (Mazzocchio et al., 2006), and running downhill reduces Sol H_{max}/M_{max} ratios more than running on a level slope (Bulbulian and Bowles, 1992). Likewise, DSW is an eccentric-biased exercise, which inherently requires greater neuromuscular and supraspinal control than concentric-biased exercises like LW (Moritani et al., 1987, Nardone et al., 1989, Nakazawa et al., 1993, Howell et al., 1995, Fang et al., 2001, 2004). Additionally, DSW challenges balance, which may promote more

supraspinal control from the reticulospinal tract or other descending pathways to stabilize posture, thereby reducing the contribution of spinal reflexes to the maintenance of equilibrium (Purves et al., 2001, Schuurmans et al., 2011). Balance training alone is associated with decreased H_{max}/M_{max} ratios and adaptation of corticospinal pathways (Taube et al., 2007). Therefore, because DSW involves eccentric muscle contractions and poses a challenge to balance and equilibrium, supraspinal pathways may contribute to H-reflex depression, likely through presynaptic inhibition (Moise et al., 2015).

Increased eccentric muscle contractions during DSW may also increase muscle spindle afferent feedback, which could cause down-regulation of the Ia-afferent/α-motoneuron synapse (Sabatier et al., 2015). For example, muscle spindles are activated when a muscle is vibrated (Burke et al., 1976), and prolonged vibration of a muscle induces H-reflex depression (Shinohara, 2005). However, our previous study found no change in post-activation depression following DSW for 20 minutes at a -15% slope (Sabatier et al., 2015). Therefore, descending pathways may be exerting greater control over the Ia-afferent/α-motoneuron synapse.

Sol H-reflexes were more depressed following DSW for 20 minutes at -25% than 10 minutes at -15% and LW, providing evidence of a dose-response relationship. DSW for 20 minutes at -25% is a more intense exercise than 10 minutes at -15%, demonstrated by greater elevations in HR and RPE during DSW at -25% compared to -15%, regardless of duration. Additionally, HR and RPE were not different during walking at -15% compared to LW, similar to our previous study that also found DSW for 20 min. at -15% is a light activity without much cardiovascular or perceived strain (Sabatier et al., 2015). Therefore, walking down a -25% decline is a more difficult exercise than walking down a -15% decline.

However, the greater reduction in Sol H-reflexes after the steeper slope is not due to increased effort, because upslope walking causes a much larger increase in HR and RPE responses yet does not produce Sol H-reflex depression (Sabatier et al., 2015). Instead, the steeper slope places a greater demand on the spinal cord due to the increased intensity of the neural patterns associated with DSW, causing more Sol H-reflex depression following the -25% slope. We could speculate further that DSW at -30% would induce even more spinal plasticity.

On the other hand, there was no effect of DSW on TA $H_{\max}/M_{\max}$ ratios. Therefore, Sol H-reflex depression following DSW is not generalizable to the TA, potentially due to different functional roles of the Sol and TA and distinct afferent feedback during DSW. In normal walking, the Sol is active during the stance phase and responsible for generating a majority of support during late stance, when plantarflexion propels the body forward. In contrast, the TA is active during the swing phase of walking, dorsiflexing the ankle against gravity and controlling the ankle in preparation for heel strike (Neptune et al., 2001, Anderson and Pandy, 2003). Therefore, the Sol is active for a longer period of time than the TA during the gait cycle (Lay et al., 2007). Additionally, ankle joint stiffness is larger during the stance phase of DSW (Shamaei et al., 2011), which helps control the body's posture from leaning too far forward. Therefore, the Sol may experience more biomechanical demands and be more sensitive to afferent feedback during DSW compared to the TA, leading to spinal plasticity.

The TA H-reflex pathway has been studied much less than the Sol H-reflex pathway, in large part because TA H-reflexes tend to be entirely absent or very small (Jusic et al., 1995). For instance, in this study, average baseline TA H-reflex amplitudes were only 11%

of M_{max}, whereas average baseline Sol H-reflex amplitudes were 59% of M_{max}, similar to findings reported by Brooke and colleagues (Brooke et al., 1997). The difficulty in measuring H-reflexes from the TA can largely be overcome by using tonic contraction of the TA while evoking H-reflexes (Brooke et al., 1997, Zehr, 2002), as done in the current study. Nevertheless, TA H-reflex amplitudes remained small, which may have made it difficult to detect an effect of DSW on TA H-reflexes because the level of inhibition that is possible for the H-reflex depends on the size of baseline H-reflex measurements (Crone et al., 1990). Therefore, the small size of the TA H-reflex may have prevented us from detecting a change following DSW.

Recurrent Inhibition

There was no significant effect of DSW on recurrent inhibition. However, there was a trend towards more recurrent inhibition following DSW for some walking conditions, demonstrating that during DSW, Renshaw cell activity may increase, but not enough to show a significant percent change after the exercise. Greater Renshaw cell activity during DSW could occur due to the need for the Sol and TA to stabilize body posture on an unsteady slope through co-contraction. Renshaw cells inhibit Ia inhibitory interneurons that relax antagonist muscles in order to facilitate co-contraction (Baret et al., 2003, Pierrot-Deseilligny and Burke, 2006). We originally thought that because DSW causes more co-contraction than LW (Lay et al., 2007), recurrent inhibition would be increased. However, we cannot conclude that recurrent inhibition increased following DSW.

We observed another trend that percent change in recurrent inhibition before and after DSW was more negative following 20 minutes of walking than 10 minutes, regardless of slope. That is, there was more recurrent inhibition after DSW for 20 minutes than 10

minutes, demonstrating a potential dose-response effect of DSW duration on recurrent inhibition. Future studies should determine if a longer duration, e.g. 30 minutes of DSW, causes a more consistent increase in recurrent inhibition, in addition to investigating other mechanisms and spinal pathways that could mediate H-reflex depression following DSW.

It is important to note that the recurrent inhibition technique can be difficult for laboratory technicians to perform. This is largely attributable to high Sol H-reflex amplitude variability when the H-reflex (H1) target amplitude is small, i.e., 10% of M_{max}. It is imperative to control H1 because recurrent inhibition is affected by the H1 amplitude (Pierrot-Deseilligny et al., 1976). That is, a larger H1 amplitude results in a larger difference between H' and H1, or more recurrent inhibition. In this study, several sessions were excluded from analysis because H1 reflexes were out of range. Another potential confounding variable in the recurrent inhibition test was low reliability across days for baseline recurrent inhibition. The cause of the low reliability is unknown. There may have been a training effect across days that shifted baseline measurements. In endurance-trained athletes, for example, recurrent inhibition is reduced compared to power-trained and untrained individuals (Earles et al., 2002), suggesting a training effect is possible. Measurement error and random effects may have also contributed to reduced reliability. For example, there may have been presynaptic adaptations that obscured changes that occurred in Renshaw cell excitability.

Clinical Relevance of Downslope Walking

This study found that DSW induces acute spinal plasticity in a dose-dependent manner. Even though HR, RPE, and muscle soreness were higher for DSW at -25%, average measures for RPE only reached "somewhat hard" and average HR did not exceed 102 bpm,

a low exercise HR. Therefore, more spinal plasticity might be induced with only a minimal increase in effort. Future research should determine if people with neurological dysfunction and spasticity who are able to walk exhibit larger responses to DSW at steeper slopes. In our previous experiments with Multiple Sclerosis, DSW at a -7.5% slope was considered easy by participants, thereby offering flexibility in exploring the dose-response effect. The results of the current study suggest progressive overload, which is the gradual increase in bodily stress during exercise, could be used in a DSW training program to maximize the neural effects while minimizing the burden. In conclusion, DSW could be an effective intervention to treat spasticity. The results of this study can be used to guide future studies to determine the long-term effects of DSW training in individuals with spasticity in order to determine the clinical viability of DSW in reducing spinal excitability and spasticity and improving quality of life.

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