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Flexor reflex decreases during sympathetic stimulation in chronic human spinal cord injury

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Abstract:

A better understanding of autonomic influence on motor reflex pathways in spinal cord injury is important to the clinical management of autonomic dysreflexia and spasticity in spinal cord injured patients. The purpose of this study was to examine the modulation of flexor reflex windup during episodes of induced sympathetic activity in chronic human spinal cord injury (SCI). We simultaneously measured peripheral vascular conductance and the windup of the flexor reflex in response to conditioning stimuli of electrocutaneous stimulation to the opposite leg and bladder percussion. Flexor reflexes were quantified using torque measurements of the response to a noxious electrical stimulus applied to the skin of the medial arch of the foot. Both bladder percussion and skin conditioning stimuli produced a reduction (43-67%) in the ankle and hip flexor torques ($p < 0.05$) of the flexor reflex. This reduction was accompanied by a simultaneous reduction in vascular conductance, measured using venous plethysmography, with a time course that matched

the flexor reflex depression. While there was an overall attenuation of the flexor reflex, windup of the flexor reflex to repeated stimuli was maintained during periods of increased sympathetic activity. This paradoxical depression of flexor reflexes and minimal effect on windup is consistent with inhibition of afferent feedback within the superficial dorsal horn. The results of this study bring attention to the possible interaction of motor and sympathetic reflexes in SCI above and below the T5 spinal level, and have implications for clinicians in spasticity management and for researchers investigating motor reflexes post SCI.

Keywords: autonomic dysreflexia, windup, spasticity.

Introduction

The purpose of this study was to examine the modulation of flexor reflex windup during episodes of induced sympathetic activity in chronic human spinal cord injury (SCI). Both autonomic and somatic reflex pathways have important clinical implications in SCI. Autonomic dysreflexia (AD), characterized by acute hypertensive events resulting from uncontrolled sympathetic reflexes, and flexor spasms, consisting of paroxysmal muscle contractions, can both contribute to disability in this patient population. Consequently, an improved understanding of the mechanisms underlying these problems and their possible interrelationship could potentially lead to improved clinical management of both AD and spasticity.

Autonomic dysreflexia is a common condition post SCI that has been clinically linked to increased muscle spasms, yet the mechanisms remain undetermined. AD can be triggered in 45-90% of individuals with quadriplegia or high paraplegia (Teasell, et al., 2000, Yarkony, 1994) by a variety of stimuli from afferent sources below the injury level including the bowel and bladder, cutaneous, and muscle receptors (Corbett, et al., 1975, Corbett, et al., 1971, Corbett, et al., 1971). Importantly, an increase in muscle spasms is commonly associated with induced sympathetic responses (Kewalramani, 1980, Riddoch, 1917) and is anecdotally reported by SCI individuals during bladder infections. A relationship between spinal autonomic and motor systems was first documented by Riddoch who coined the term "mass reflex" to describe AD (Head and Riddoch, 1917, Riddoch, 1917). This term arose from the increase in the severity and frequency of flexor

spasms during bouts of AD induced by bladder distention, suggesting a link between autonomic and flexor reflex pathways.

Following these early observations of flexor spasms during episodes of increased sympathetic activity, several investigators have examined the role of bladder distention and prolonged cutaneous stimulation on lower extremity flexor reflexes. Bladder distention in acute spinal cats results in a facilitation of an induced flexor reflex (Evans and McPherson, 1959). Similarly, spontaneous flexor spasms are known to coincide with detrusor contractions in chronic human spinal injuries (Pedersen, et al., 1986). In contrast, a study of noxious stimulation induced flexor reflexes during bladder distention in humans with neurological conditions, including chronic SCI, reported either facilitation or inhibition of the flexor EMG (Mai and Pedersen, 1976). Noxious cutaneous stimulation has been shown to produce AD (Corbett, et al., 1971) and lower extremity vasoconstriction in high and low level injuries (Garrison, et al., 2008), yet there are no studies of its concurrent influence on flexor reflexes. While the sympathetic response was not monitored, several studies of electrical stimulation of peripheral nerves have shown inhibition of flexor reflexes in human SCI (Gregoric, 1998, Roby-Brami and Bussel, 1992). These contradictory findings of facilitation and inhibition may stem from differences in completeness and chronicity of the spinal cord lesion as well as the array of afferent pathways thought to be involved in flexor spasms.

In SCI, flexor spasms consisting of hip and ankle flexion are often observed in response to exteroceptive stimuli and may be associated with an increase in the baseline excitability of the flexion withdrawal reflex (Young and Shahani, 1986). Hyperexcitability of the flexion withdrawal reflex is evidenced by decreased thresholds to electrocutaneous stimuli and increased EMG responses in human SCI (Dimitrijevic and Nathan, 1968, Shahani and Young, 1971). Besides cutaneous A δ and C fiber afferents, there is evidence for muscle afferent input (group III-IV and possibly non-spindle group II fibers) based on flexor reflexes imposed by movements of the ankle (Schmit, et al., 2002) and intramuscular stimulation (Hornby, et al., 2003). Regardless of the afferent source, Jankowska has proposed that the increase in excitability of flexor reflex pathways following SCI is due, at least in part, to the loss of descending inhibition from

monoaminergic pathways (Jankowska and Hammar, 2002). This change in neuromodulation could contribute to windup of flexor reflexes, consisting of a buildup of the flexor reflex response to successive noxious skin stimuli, which has been observed in chronic human SCI (Dimitrijevic and Nathan, 1970, Hornby, et al., 2003). One benefit of studying the windup phenomenon is that it provides indirect insight into the flexor reflex spinal circuitry based on the reduced preparation evidence for windup in motoneurons (Bennett, et al., 2004) or deep dorsal horn interneurons (reviewed in (Hornby, et al., 2003).

In the current study, we examined the windup of flexor reflex torque and EMG responses to repeated noxious skin stimuli applied to the arch of the foot. Modulation of the flexor reflex during contralateral noxious skin stimuli and bladder percussion was measured, along with the vascular conductance of the contralateral leg as a measure of the sympathetic response. This provided a controlled test of flexor reflex modulation by two dissimilar stimuli that both produced sympathetically mediated lower extremity vasoconstriction.

Materials and Methods

Subjects

Eight volunteers with SCI were recruited for participation in this study. All subjects were at least 2-years post injury and lacked sensation and volitional motor control of the lower extremities, (American Spinal Injury Association (ASIA) classification A). Additional subject characteristics including injury level, gender, and medications are listed in Table 1. Subjects were used as their own controls to eliminate the need to alter medication dosage or schedule, prior to the experiments. None of the subjects were smokers and consumption of caffeine and alcohol was avoided prior to each experiment. Exclusion criteria included unhealed pressure sores, bladder or other infection, and hypertension. Informed consent was obtained from all subjects prior to participation in the study. The experimental protocol was approved by the Marquette University IRB and adhered to the principles of the Helsinki Declaration of 1975.

Subject Number	Injury level	Age	Time post injury (yrs)	Gender	Medications
1 ^{*Δ}	T6	24	3	M	None
2 ^{*Δ}	T6	24	4	M	Oxybutynin, Imipramine
3 ^{*Δ}	T6	39	13	M	Baclofen, Oxybutynin
4 [*]	T8	43	24	M	Oxybutynin
5 [*]	C6-7	48	22	M	None
6 [*]	C7-T1	20	2	F	Baclofen
7 ^{*Δ}	T3-5	32	4	M	Baclofen, Tolterodine, Imipramine
8 ^{*Δ}	T6	47	6	M	Baclofen/morphine pump, Neurontin

Table 1 Subject Characteristics

*Denotes participation in skin stimulation experiment

ΔDenotes participation in bladder percussion experiment

Experimental Procedures

Subjects were seated in a semi-reclined position with both legs elevated to heart level and the extremities were supported and stabilized to prevent movement. Static joint angles ranged from 70-90 degrees of hip flexion, 130-140 degrees of knee flexion, and 0-15 degrees of ankle plantarflexion, depending on the available range of motion. For quantification of flexor reflex torques, the right foot was secured to an instrumented footplate. Right leg joint angle and body segment length measurements were recorded for each subject and used for joint torque calculations. A six-axis load cell (JR3, Woodland, CA) provided measurements of the two forces and moment that were used to calculate the static, sagittal plane, joint torques of the ankle, knee and hip.

Surface electromyogram (EMG) measurements of the right leg muscles were made for the purpose of confirmation of torque measurements and for validating estimates of individual muscle activity. Surface EMGs were recorded from the tibialis anterior, soleus and medial gastrocnemius. After preparing the skin, active preamplifier electrodes were applied over the respective muscle bellies, and shielded leads were attached to an AMT-8 Octopus EMG amplifier

(Bortec, Calgary, Alberta, Canada) with amplification of 1000 and bandpass filtering (10Hz-1.5kHz).

In order to measure sympathetic reflexes produced by bladder percussion and noxious skin conditioning stimuli, arterial flows of the left leg were recorded with a venous plethysmography system (EC6, D.E. Hokanson Inc, Bellevue, WA). The system consisted of a mercury-in-silastic strain gauge placed around the largest circumference of the calf. A venous occlusion cuff was placed around the thigh and connected to a rapid inflator set at 55mmHg. The inflation duty cycle was controlled by a digital pulse from the computer, producing 8s of inflation followed by 12s of rest to allow for flow measures every 20s. A second cuff was placed just proximal to the ankle and was manually inflated to suprasystolic pressure for the duration of the experiment. These flow measures were alternated with a flexion reflex stimulus in order to minimize movement artifact. Although arterial flow was measured during both bladder percussion and noxious skin conditioning stimulation of the left leg, muscle contractions associated with the noxious skin conditioning stimulus sometimes produced artifacts that precluded meaningful results. Previous studies with contralateral stimulation indicate that noxious cutaneous conditioning stimulation consistently produces an immediate and robust sympathetic reflex in the contralateral lower extremity (Garrison, et al., 2008).

Measures of the flexion reflex response were made in the 12s interval between venous plethysmography measurements. Flexion reflexes were elicited using a stimulus applied to the medial arch of the right foot. A pair of Ag-AgCl, 2.5 cm square pregelled electrodes (Vermed, Bellows Falls, VT) was placed on the medial arch of the foot, spaced approximately 3cm apart. The stimulus was delivered using a Digitimer constant current stimulator (Model DS7A, Digitimer Ltd., Hertfordshire, England), triggered from the experiment control computer. Test stimuli consisted of a 200Hz pulsetrain of 1ms duration pulses applied for 50ms (i.e. 10 pulses). The stimulus amplitude was set to 50mA, a stimulus that typically generated a vigorous response (ankle torque > 5Nm). A total of 3 stimuli were applied at a 1s interval to obtain a measure of windup of the flexor reflex response (Hornby, et al., 2003, Schmit, et al., 2003). The rationale for using 3 stimuli was that windup stabilizes by the 3rd stimulus (at interstim intervals

less than 5s.) and begins habituation by the 5th stimulus (Hornby, et al., 2003).

An Ohmeda 2300 Finapres (Ohmeda, Englewood, CO) was used to continuously monitor blood pressure. A cuff transducer was secured around the middle phalanx of the third digit while the arm and hand were supported so that the hand was resting at heart level. The pressure waveform provided a measure of systolic and diastolic pressure while mean arterial pressure and heart rate were calculated offline. All noxious stimuli were withdrawn and the experiment terminated if blood pressure exceeded 180/110 mmHg (for those with injuries above T6).

For the first set of experiments (n=8), the sympathetic reflex response was elicited by a conditioning stimulus consisting of noxious electrocutaneous stimulation applied to the medial arch of the left foot (opposite the flexor reflex test leg) through a pair of Ag-AgCl 2.5cm square pregelled electrodes (Vermed, Bellows Falls, VT). A Digitimer stimulator (Model DS7A, Digitimer Ltd, Hertfordshire, England) was computer controlled to deliver a continuous electrical stimulus (40mA, 25Hz, 1ms pulse width) for 90s during the 'conditioning phase'. The conditioning stimulus was initiated between sequential flexion reflex responses with an approximate 10s lead time. The protocol consisted of 90s of baseline recordings (4 flow and 4 flexor reflex trials), 90s of constant electrical conditioning stimulation applied to the left leg (4 flow and 4 flexor reflex trials) followed by 90s of post-stimulus testing (4 flow and 4 flexor reflex trials).

Because of possible crossed extension effects of the conditioning stimulation on the flexion reflex, the protocol was repeated, on a separate occasion, in 5 subjects using bladder percussion. Bladder percussion has been shown to elicit sympathetic responses in both high and low level SCI (Karlsson, et al., 1998, Mathias and Frankel, 1988). In order to provide a controlled stimulus, a custom bladder percussion apparatus was built. A small motor with eccentrically weighted shafts was housed in a plastic casing. The motor rotated four revolutions (4200 rpm) and the inertial effect upon stopping created a forceful percussion sensation. The device was strapped over the bladder just superior to the pubic crest and taps occurred at a frequency of 1 or 3 Hz for a 120s duration. The duration of the bladder

percussion was longer than the skin stimulation because preliminary experiments demonstrated a delayed onset of the response to bladder percussion in some subjects. As a result, the second protocol consisted of a 90s baseline phase, 120s of bladder percussion (6 flow and 6 flexor reflex trials), and 90s post-stimulus testing.

Data Acquisition and Analysis

Control of venous plethysmography, noxious stimulation, and bladder percussion were implemented using custom LabVIEW (National Instruments, Austin, TX) software. Control signals were generated as TTL waveforms and sent to the respective devices to assure precise timing. All measured signals were low pass filtered (4 pole Butterworth) at 450 Hz before being sampled at 1000 Hz (6071E A/D board, National Instruments, Austin, TX) using the same computer system. A total of 10 channels were recorded including: 3 load cell, 3 EMG, blood pressure, venous plethysmography, and 2 stimulation triggers.

Offline processing of the raw force and torque data included calibration and 10 Hz low pass filtering with a 4th order, zero delay, Butterworth filter (*butter/filtfilt* Matlab commands; Mathworks, Natick, MA). Joint torques were then calculated with a standard mechanical analysis, using a free body diagram (Schmit, et al., 2000). Trapezoidal numerical integration (*trapz* Matlab command) was used to calculate the areas under the hip and ankle joint torque curves over a 1s window and these values were used as the dependent variables. The knee torque was not used for further analysis since it yields inconsistent patterns in subjects with SCI (Deutsch, et al., 2005).

The blood pressure waveform was 10 Hz low pass filtered and an event detection algorithm was used to identify the systolic and diastolic deflections. Mean arterial pressure $[(\text{systolic}-\text{diastolic})/3 + \text{diastolic}]$ was calculated and used to determine calf arterial conductance. Arterial flow, with units of ml/100ml/min (or %/min), was determined by calculating the slope of the plethysmography volume curves during the middle 6s of each 8s inflation period. The flow was divided by the mean arterial pressure (averaged over the corresponding time interval) to provide the arterial conductance during each 6s window of time. The first flow values were discarded to

account for cuff settling, leaving 3 measures of baseline conductance, along with 4-6 measures during the conditioning stimulus and 4 measures after the stimulus.

EMG signals were processed by a 4th order Butterworth notch filter (58-62 Hz) to remove 60 Hz line noise followed by low pass filtering with a 10th order Butterworth filter at 120Hz (*butter/filtfilt* Matlab commands) to remove most of the artifact introduced from the electrocutaneous stimulation (25 Hz and harmonics). Signals were then rectified and displayed.

Statistics

The normalized magnitude of the flexor reflex integrated ankle and hip torques were compared across baseline, conditioning, and post-conditioning trials. The flexor reflex paradigm used in this study demonstrated habituation over the first two sets of windup trials. This habituation has been reported previously and is followed by a stable period that can extend for several minutes when tested at intervals of 20 seconds (Fuhrer, 1976). As a result, the first two flexor reflex trials were excluded from analysis and the baseline response was composed of the two trials preceding the onset of conditioning stimulation. An average for each windup response (stimuli 1-3) was obtained from the two baseline trials and was used to normalize the respective torque responses for all subsequent trials.

Statistical comparison of the conditioning phases was done using specific individual flexor reflex trials. Specifically, these trials included the pre-conditioning phase (PRE): the trial immediately before the onset of the conditioning stimulus; the conditioning phase (COND): the trial with the peak depression of the 1st flexor reflex response of the windup train; and the post-conditioning phase (POST): the last trial of the experiment (~70 seconds post conditioning). The normalized hip and ankle integrated torque values were compared across windup response (stimuli 1-3), phase (PRE, COND or POST) and conditioning type (electrical stimulation – bladder tapping) using a MANOVA ($\alpha = 0.05$) followed by univariate analysis (ANOVA) when significant. In order to determine where specific differences lay, two-way ANOVAs were used to compare integrated torque for each joint and conditioning type across phase and windup response. Tukey's

pairs comparisons were used when significance was found for phase ($\alpha = 0.05$).

The results of subject 8 were presented for discussion but were not included in the analysis because this subject was taking narcotic analgesics that are known to have significant depressor effects on the flexor reflex (Hu, et al., 1999, Willer and Bussel, 1980). In addition, technical difficulties excluded subject 7 from analysis during the skin stimulation experiment. Therefore, the sample sizes were reduced for both skin stimulation, $n=6$, and bladder percussion, $n=4$.

Results

In the present study, we examined the modulation of flexion withdrawal responses during induced sympathetic reflexes in subjects with chronic, complete SCI. Both skin stimulation and bladder percussion produced a clear depression of the flexor reflex. The group data for the normalized hip and ankle torque responses were compared statistically for the PRE, COND, and POST phases and for both types of conditioning stimuli.

Representative Data: Torque

Figures 1 and 2 represent the salient features of the torque responses for skin stimulation and bladder percussion conditioning, respectively. The figures display the filtered torque curves over a 1s window following each flexor reflex stimulus. The curves demonstrate not only a decrease in peak torque during conditioning but also a change in the rise time and duration of the response. As a result, integrated torque was used for statistical analysis because it better reflected the overall changes in torque. The baseline responses (trials 1-2) were followed by marked depression of the torque curves during the conditioning trials (3-6 for skin stimulation and 3-8 for bladder percussion). Recovery of the response back towards baseline often began at the end of the COND phase and continued into the POST phase (trials 7-10 or 9-12). Differences in degree of depression and recovery varied between ankle and hip within subjects (Fig. 1). The changes in the windup of the flexor reflex can also be clearly seen in these figures. Across trials, the 2nd and 3rd windup responses typically

followed the first response but sometimes the windup did not recover as strongly (Fig. 2).

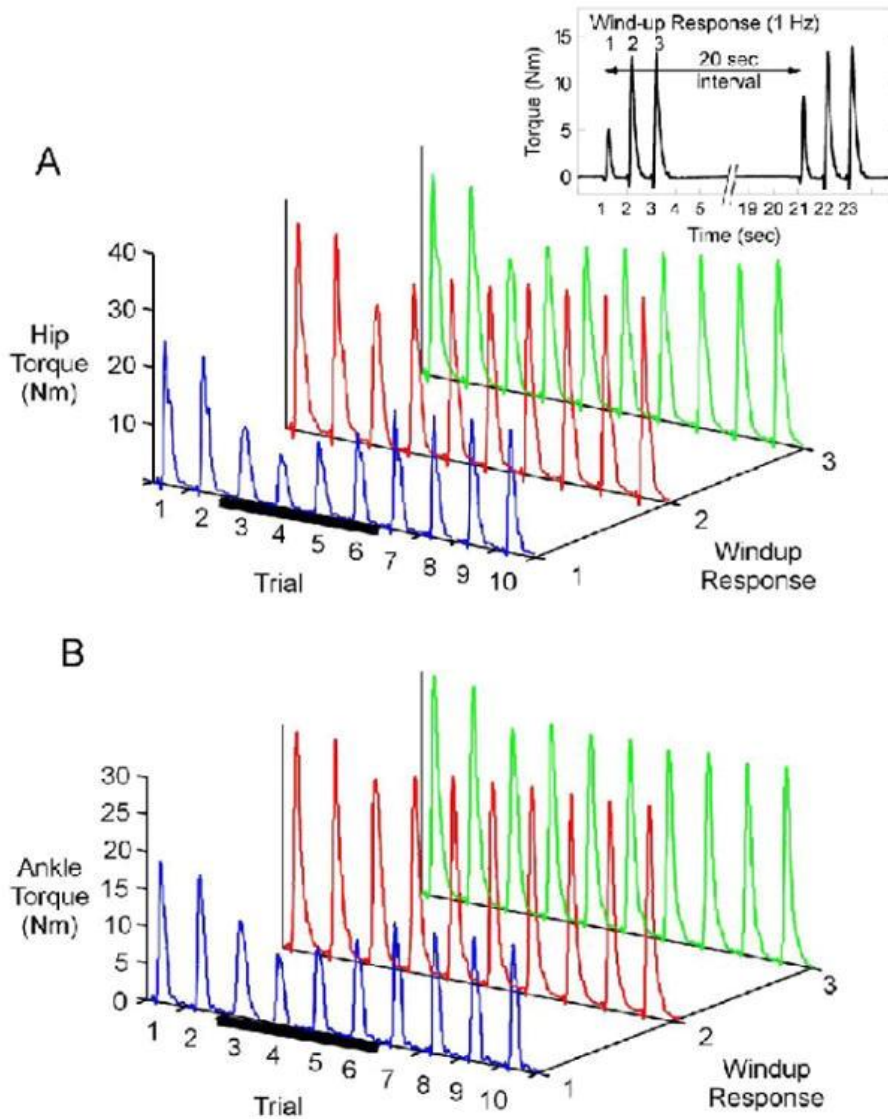


Figure 1 Conditioning effects of contralateral foot skin stimulation on flexor reflex responses are shown for a representative subject (Subject 2). Responses are segmented and plotted as separate traces to demonstrate the windup response (z axis) and the effect across time (x axis). The inset at top right shows the flexor reflex stimulus paradigm (a 200Hz pulsetrain of 1ms duration applied for 50ms with the stimulus amplitude set to 50mA). Each trial consisted of 3 flexor reflex responses (windup) tested at 1s intervals with 20s between trials. Flexion torque over a 1s duration is shown for each windup response and trial. The conditioning phase (90s duration, 40mA, 25Hz, 1ms pulse width stimulus) is denoted by a solid black bar (trials 3-6). A. Hip torque shows a large decrease in both the first response (blue) and

the windup (red and green) during conditioning with partial recovery post conditioning. B. Ankle torque shows a similar pattern of depression and recovery of the first pulse across trials.

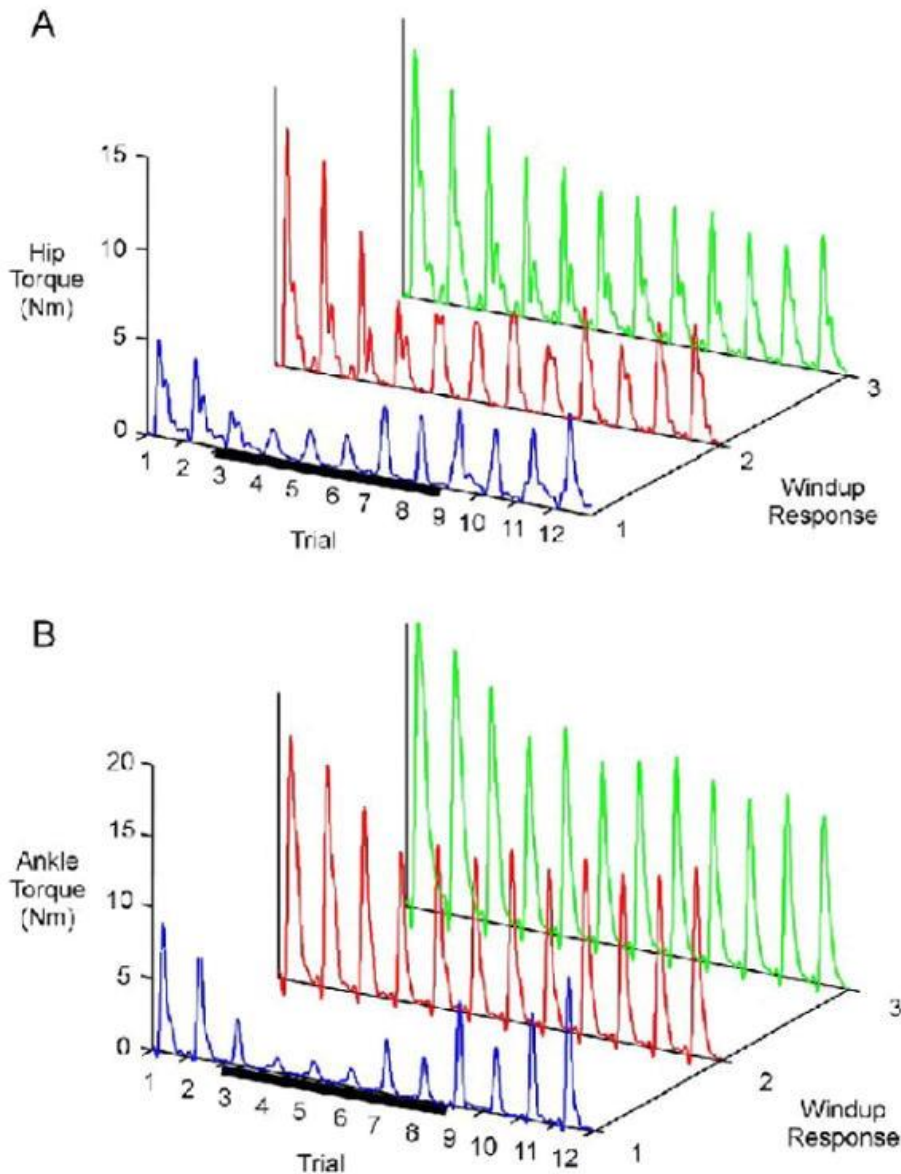


Figure 2 Effect of bladder percussion on flexor reflex responses is shown for one subject (Subject 1). Responses are segmented and plotted as separate traces to demonstrate the windup response (z axis) and the effect across time (x axis). Each trial consisted of 3 flexor reflex stimuli (a 200Hz pulsetrain of 1ms duration applied for 50ms with the stimulus amplitude set to 50mA) tested at 1s intervals with 20s between trials. Flexion torque over a 1s duration is shown for each windup response and trial. The conditioning phase (120s duration, mechanical percussion at 1 or 3 Hz)

is denoted by a solid black bar (trials 3-8). A. Hip torque shows a large decrease in both the first response (blue) and the windup (red and green) during conditioning with partial recovery of the first response. Windup did not tend to recover as strongly in this subject. B. Ankle torque shows a similar pattern of depression of the first pulse but less depression of the windup responses.

Representative Data: Electromyography

EMG of the lower extremity muscles was not used in the comparison of the conditioning effect on the flexor reflex because of the large amount of noise introduced from the conditioning skin stimulus. However, the EMGs were useful for confirmation of the relative contribution of the ankle muscles to the torque response. One concern was that the decrease in dorsiflexion torque might be due to an increase in antagonist (medial gastrocnemius, soleus) contraction rather than a decrease in the agonist (tibialis anterior). In fact, studies have reported that the flexor reflex response in SCI is often accompanied by cocontraction of the ankle musculature (Dimitrijevic and Nathan, 1968, Xia and Rymer, 2005). Figure 3 shows the filtered and rectified EMGs from the tibialis anterior (TA) medial gastrocnemius (MG) and soleus (SO) muscles in subject 5. Although there was some plantarflexor activity during the PRE phase (Fig. 3B&C), it decreased along with the TA during conditioning (Fig. 3A). This pattern was confirmed in the other subjects as well and served to support the torque evidence demonstrating a depression of the flexor reflex during sympathetic conditioning.

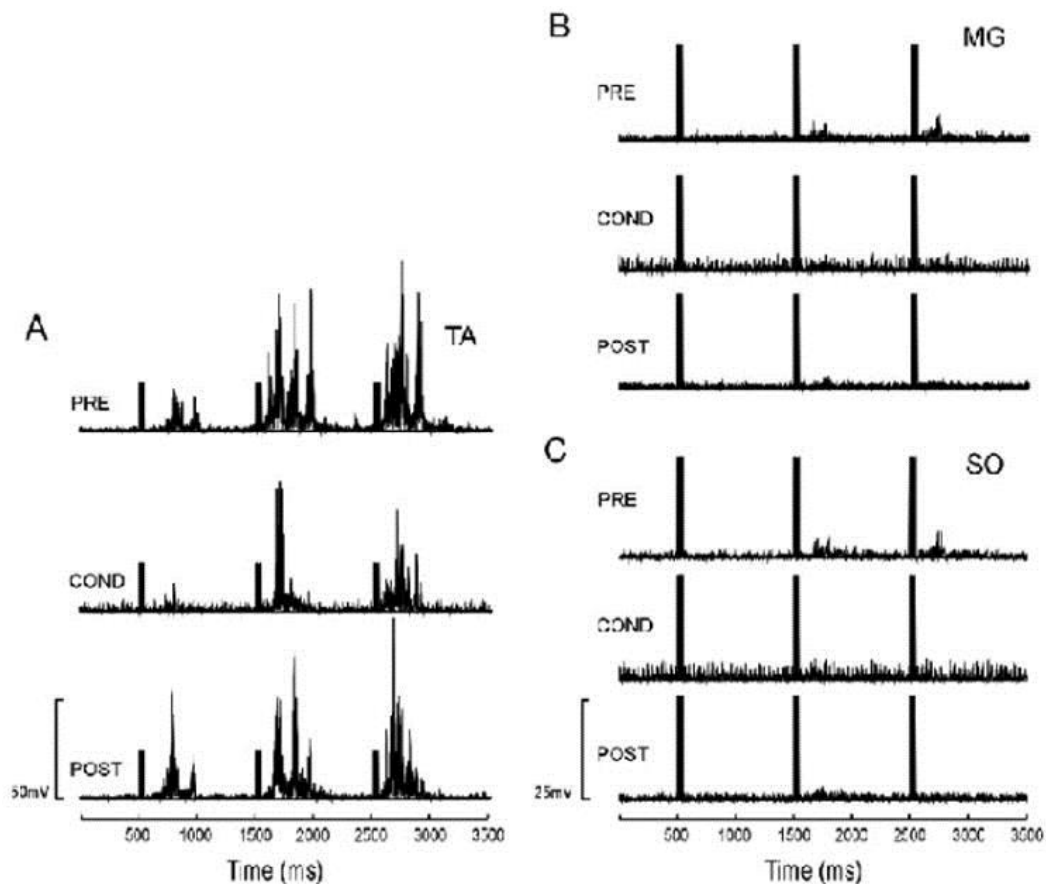


Figure 3 The filtered and rectified EMG of the ankle muscles (medical gastrocnemius (MG), soleus (SO) and tibialis anterior (TA)) is shown for subject 5. Representative trials, as described in the text, are presented from each phase (PRE, COND, and POST). The vertical bar indicates the trigger for the flexor reflex stimulus. A. A clear decrease in TA activity was seen during COND with partial recovery in the POST phase. B-C. While there was antagonist cocontraction in the PRE phase, it was virtually eliminated in the COND and POST phases. This confirmed that the depressed ankle torque response was not due to increased antagonist activity. Finally, windup was evidenced in all phases by the increased amplitude and decreased latencies in the EMG across responses 1-3.

Figure 4 shows the normalized integrated torque responses to the first flexor reflex stimulus across all trials. For this analysis, the individual trials were normalized by the mean of the preconditioning responses for each subject. Individual subject hip and ankle responses are shown for skin stimulation (Fig. 4A & C) and bladder percussion (Fig. 4B & D). A clear depression of the multijoint flexor reflex was observed in all subjects with varying degrees of recovery. These data

were used as the dependent variable for the group analysis comparing the effects of conditioning type, phase, and windup response on the flexor reflex.

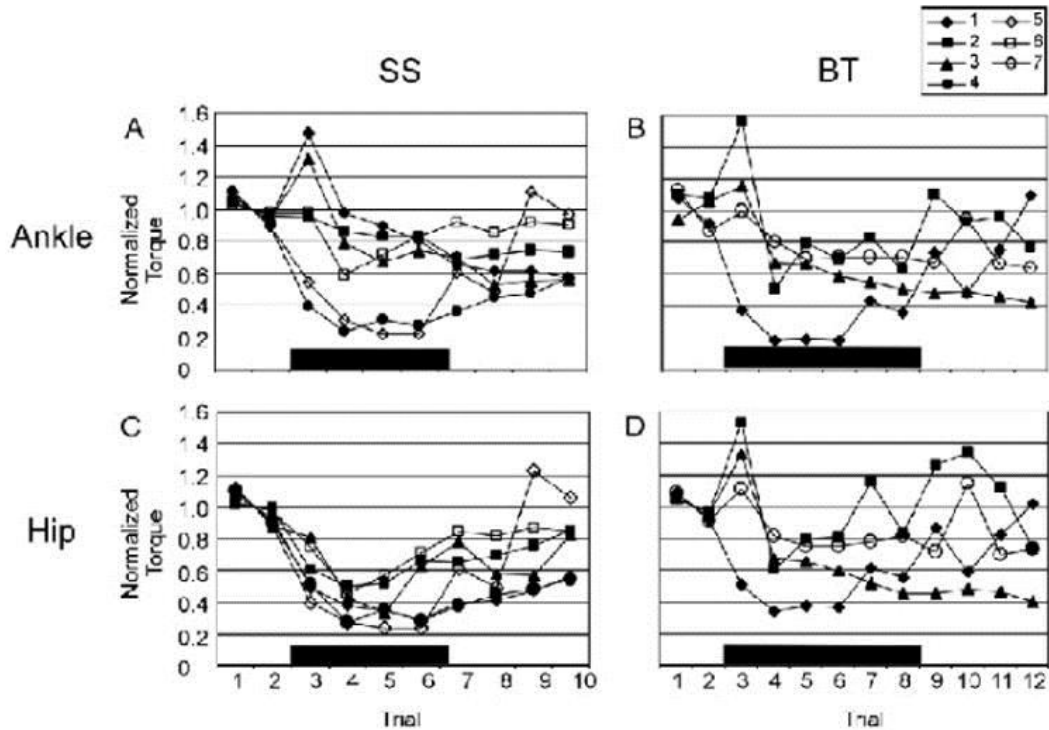


Figure 4 The normalized, integrated torque responses for all subjects are shown. The first ankle and hip torque response of all trials was normalized by the baseline and plotted for skin stimulation (SS) and bladder percussion (BT). The black bar denotes conditioning trials. Subject numbers correspond to Table 1. The largest flexor reflex depressions were in subjects (1, 4, & 5) not taking baclofen or imipramine (although not statistically different). All subjects demonstrated a decrease in flexor reflex response during conditioning with varying degrees of recovery. Individual differences were seen with some subjects demonstrating increased torque on the first response (A,B,D) but this was not evident at all joints (C).

One subject, #8, failed to show any depression of the flexor reflex during skin or bladder stimulation (Fig. 5). His removal from further analysis was justified on the basis of his exclusive use of narcotic analgesics.

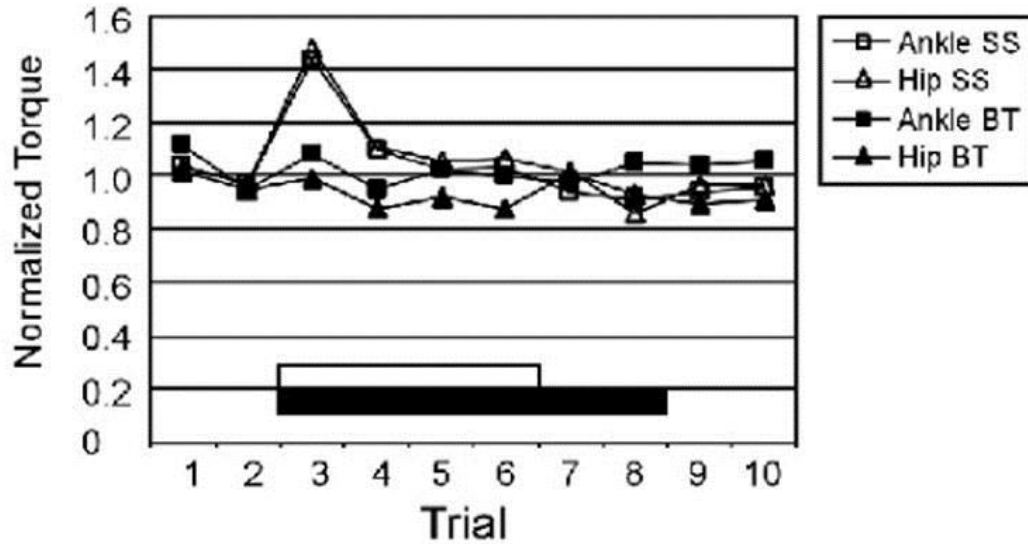


Figure 5 Subject 8 failed to demonstrate a depression of the flexor reflex. The ankle and hip torque responses are shown for skin stimulation (SS) and bladder percussion (BT). This unique response was attributed to a medication effect, as he was the only subject on morphine. See text for discussion.

MANOVA

Based upon the results of the MANOVA, the conditioning stimuli produced a significant change (reduction) in the joint torques associated with the flexor reflex responses. The results of the MANOVA on the integrated hip and ankle torques demonstrated a significant difference (Wilks criterion, $p < 0.05$) for phase (PRE, COND, POST), conditioning type (skin stimulation, bladder percussion) and a phase*conditioning type interaction. The mean normalized, integrated torque data are shown in Figure 6. There was a reduction in both hip and ankle torque during the COND and POST periods and the skin stimulation appeared to produce a greater reduction than bladder percussion.

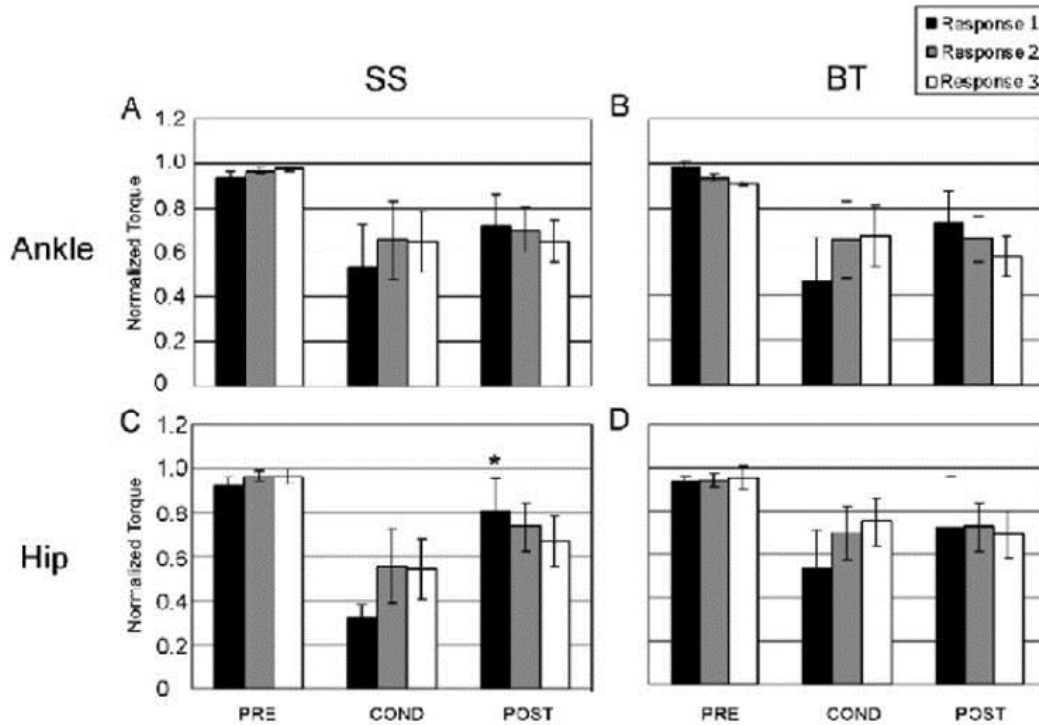


Figure 6 Group averages of integrated hip and ankle torque are shown. The mean windup responses (1-3) with 95% confidence intervals were compared across phase (PRE, COND, POST) for each joint and conditioning type (skin stimulation = SS; bladder percussion = BT). COND and POST were significantly different from PRE ($p < 0.05$) for all joints and conditioning type (A-D). An additional significant difference was found in response 1 between POST and COND phases during skin stimulation (denoted by *, $p < 0.05$) (C). There was a trend for the first flexor reflex response (response 1) to be depressed to a greater extent than the windup responses 2-3 but no significant difference was found.

Both conditioning types had a significant depressive effect on the flexor reflex response based on hip and ankle flexor torque measurements (Fig. 6). Separate univariate analyses of the hip and ankle torques revealed that the effect of conditioning type (skin stimulation, bladder percussion) was significant for hip torque only (ANOVA, $p < 0.05$), with a greater reduction in torque during skin stimulation. Main effects for hip were also found for phase and phase*windup response interaction, with lower mean values for COND and POST phases compared to PRE and a greater reduction in the first response of the windup sequence during COND, compared to the second and third stimuli. These effects are reflected in Figure 6C & D. Univariate analysis of ankle torque showed a main effect for phase

only ($p < 0.05$), with lower torques in the COND and POST phases compared to the PRE. Further analysis was done to determine where the specific differences in phase and windup response existed for each conditioning type.

Skin Stimulation

Conditioning stimulation applied to the skin of the left foot produced a simultaneous reduction in somatic blood flow (sympathetic reflex) and reduction in flexor reflex response. Specifically, the ankle and hip torques were significantly lower in COND and POST phases compared to PRE (Tukey's post hoc analysis, $p < 0.05$) and the torques for COND were significantly lower than POST for the hip, (Tukey's test, $p < 0.05$) (see Fig. 6C). The mean results showed a depression of both the ankle and hip responses followed by partial recovery, although individual differences did exist (e.g. see Fig. 4A & C). For the ankle torque, 3/6 subjects demonstrated recovery while 6/6 subjects showed recovery of hip torque. In addition, two subjects (1 & 3) had increased ankle torque in the first trial following the onset of conditioning while hip torque was depressed in the same trial. For those subjects with valid flow measures during skin stimulation (subjects 2, 4, & 5) ($n=3$), there was a clear depression of conductance followed by a recovery of 85% of the baseline conductance (range 65%-114%). A representative plot of conductance and hip flexor reflex torque during skin stimulation is shown in Figure 7A for subject 5.

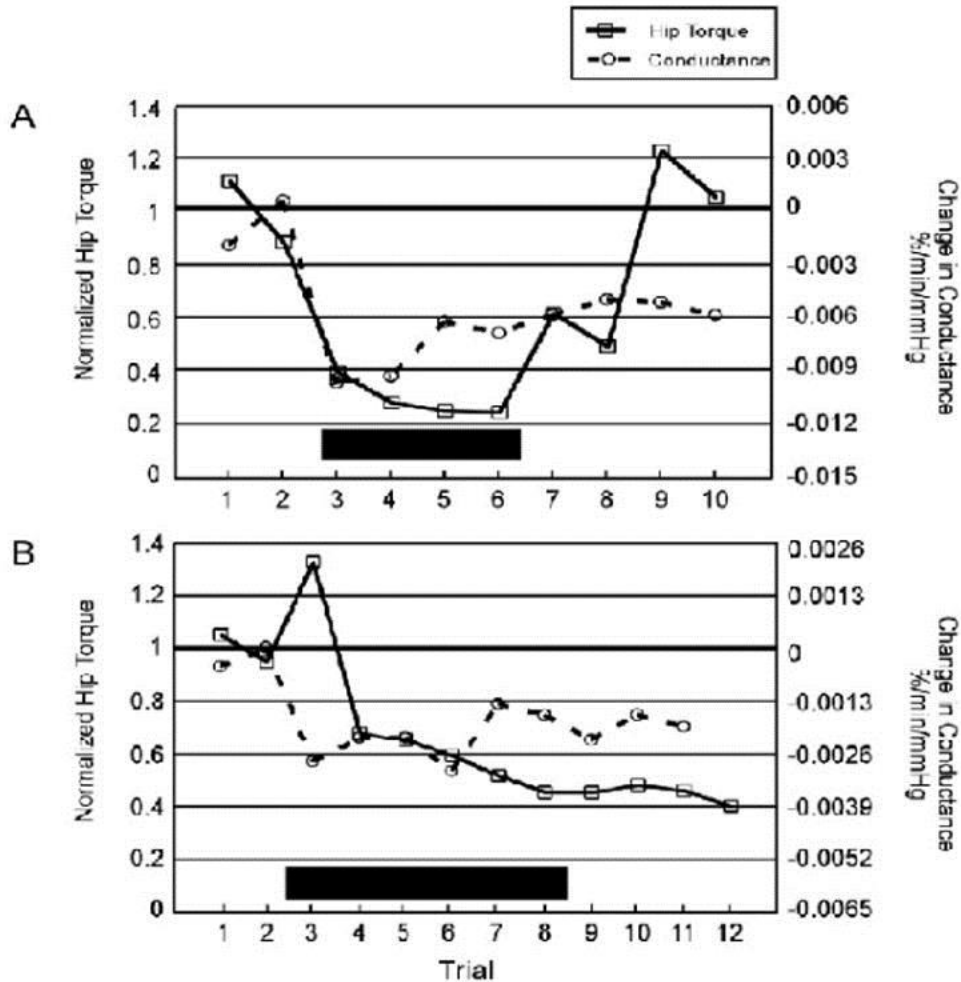


Figure 7 The decrease in flexor reflex torque appeared to correspond to the decrease in conductance. The relationship between normalized hip torque (left ordinate) and absolute change in conductance (right ordinate) across trials is plotted. In order to avoid movement artifacts, a 6s delay existed between conductance and torque measures for each trial. The black bar along the abscissa denotes the conditioning period. A. During skin stimulation, subject 5 demonstrated a large recovery of both flexor reflex torque and arterial conductance after the stimulus is withdrawn. In contrast, subject 3 did not demonstrate much recovery of either flexor reflex or conductance following bladder percussion (B). These data support the hypothesis that increased sympathetic reflexes may result in a modulation of the flexor reflex.

Bladder Percussion

The same general results were found for bladder percussion as skin stimulation, with a reduction in the flexor reflex response during

and after a sympathetic response induced by the bladder percussion. Both ankle and hip torques demonstrated a main effect for phase, with COND and POST significantly lower than PRE (Tukey's post hoc analysis, $p < 0.05$) (see Fig. 6B & D). Variability in recovery of the torque responses in the POST trials was also seen in the bladder percussion experiments. Evaluation of the individual plots (Fig. 4B & D) revealed that hip and ankle torque did not recover following conditioning stimulation for subjects 3 and 7, while some recovery of torque was evident in the other 3 subjects. This difference in recovery was consistent with a prolonged sympathetic effect for bladder percussion compared to skin stimulation. Accordingly, subject 3 had only a 31% and subject 7 a 32% recovery of conductance following bladder percussion (Fig. 7B). This contrasted with subject 1, who had an 85% recovery in conductance following conditioning and showed a strong recovery of the flexor reflex as well.

Discussion

The main findings of our study were as follows. (i) Flexor reflex responses were transiently depressed during periods of increased sympathetic reflex activity induced by bladder percussion and noxious cutaneous stimulation. The decreased flexor reflex associated with diverse conditioning stimuli could be associated with a common afferent drive to both the motor and sympathetic systems, or could be attributed to an interaction of sympathetic motor systems at the spinal level. (ii) Windup of the flexor reflex response persisted during the conditioning period. While all responses were attenuated during conditioning, the second and third windup responses showed a lesser degree of depression. This pattern could be indicative of inhibition of the flexor reflex afferents early in the flexor reflex pathways rather than in the deep dorsal horn interneurons or motoneurons where windup of the flexion reflex is thought to occur (Hornby et al. 2003, Schmit et al. 2003).

The occurrence of flexor reflex depression during bladder percussion as well as contralateral cutaneous stimuli is consistent with the notion that the flexor reflex depression is related to the activation of spinal sympathetic pathways. The alternative explanation of separate, but parallel activation of sympathetic and motor reflexes is also possible, but appears less likely. For example, contralateral

stimulation of the foot cutaneous afferents could result in a crossed extension reflex that inhibits the flexor reflex responses. Although we did not see increased EMG of the extensor muscles (Fig. 3), this does not preclude the presence of an inhibitory effect on the flexors, since facilitation of extensor muscles is often too weak to evoke EMG activity (Roby-Brami and Bussel, 1990). However, the significance of the crossed extension reflex in chronic human SCI is unclear, since many individuals display crossed flexion reflexes (Corbett, et al., 1971, Dimitrijevic and Nathan, 1968). More importantly, bladder percussion elicited quantitatively similar flexor reflex depression (Fig. 4) without the possible confounding effects of crossed extension.

Role of Fatigue / Habituation

Muscle fatigue and flexor reflex habituation may have accounted for a small portion of the flexor reflex depression, particularly in the post-stimulus period. Although habituation of the flexor reflex occurs at short time intervals in human SCI (Dimitrijevic, et al., 1972, Dimitrijevic and Nathan, 1970, Granat, et al., 1991), at the longer intervals similar to those used in this study, habituation is minimal (Fuhrer, 1976). We did observe a drop in the flexor reflex response between the first and second stimulation sequences, but the effect leveled, and the data from the initial 2 stimulation sequences were not included in the analysis. Note that the application of electrocutaneous stimuli at different locations and bladder distention have both been found to cause a dishabituation of the flexor reflex (Granat, et al., 1991, Griffin and Pearson, 1968), which might account for the increase of the first flexor reflex response that is seen in some subjects shortly after the onset of the conditioning stimulation (Fig. 4). Muscle fatigue can also contribute to reduction in the flexor reflex response with repeated stimuli; however, most subjects showed recovery of the torque responses in the post-conditioning period. The presence of partial recovery post-stimulation makes it clear that habituation and/or fatigue do not fully account for the flexor reflex depression.

Medication Effects

It is difficult to draw any conclusions regarding possible medication effects given the small number of subjects, but there were several trends to note. For those taking baclofen and/or imipramine

(subjects 2, 3, 6 and 7), there was a trend of less depression of the flexor reflex (Fig. 4) than those without any medications (subject 1 and 5) or taking oxybutynin alone (subject 4). Baclofen, a GABA agonist, is prescribed for spasms while imipramine, a tricyclic antidepressant, is prescribed for bladder management; however, both medications also have antinociceptive effects in the spinal cord (Chen, et al., 2004, Hammond and Washington, 1993) which may have affected the degree of flexor reflex depression. A second, more pronounced effect was noted in the only participant taking narcotic analgesics (i.t. morphine and p.o. Neurontin). The response of subject 8 was different from all the others in that he failed to show a depression of the flexor reflex for either BT or SS (Fig. 5). It is possible that the lack of depression could be a floor effect, i.e. intrathecal morphine could bind opioid receptors so that further depression could not be significantly affected by endogenous opioid release (Yaksh, 1988). Further testing in animal models would be necessary to substantiate this idea.

Effects on Windup

While the depressive effects on the first pulse of the flexor reflex are clear, interpreting the effects on windup is more difficult. Windup responses 2-3 were typically depressed to around 60% of the baseline values during conditioning (Fig. 6), which was less than the mean reduction in the first response, but not significantly different, except at the hip during skin stimulation (Fig. 6C). These observations suggest a generalized depression of the flexor reflex, with relatively little change in the windup effect. Windup of flexor reflexes appears to be associated with wide dynamic range, deep dorsal horn interneurons, since there is a reduction in latency during windup that is consistent with excitation by faster conducting afferents (Hornby, et al., 2003). In addition, changing the stimulation dermatome between the 2nd and 3rd stimuli of a windup sequence maintains the windup effect, consistent with a deep dorsal or ventral horn windup site (Schmit, et al., 2003). As a result, the disproportionate effect on windup in the current study is consistent with a depression of the flexor reflex early in the flexor pathways, i.e. the superficial dorsal horn, rather than the deep dorsal or ventral horn.

Evidence for Sympathetic and Motor Interactions

In this study we noted that the time course of the flexor reflex depression generally followed the sympathetically mediated conductance changes (Fig. 6) and it is tempting to postulate that there might be a common mechanism for these observations. Although there is ample evidence of coordination of the motor and sympathetic systems at the brainstem level (for a review see(Kerman, 2008), there is an increased interest in possible coupling between autonomic and motor systems at the spinal level (Deuchars, 2007). Intraspinal coupling of sympathetic and motor systems is supported by the observation of NMDA-induced correlated motor and sympathetic output in a perfused trunk-hindquarters preparation of the adult mouse (Chizh, et al., 1998). Similarly, *in vivo* measurements in the rat cervicothoracic spinal cord (spinalized at C1) exhibit correlated sympathetic and motor activity in the presence of intrathecal GABA-A antagonists (Goodchild, et al., 2008). Thus, spinal interneurons common to sympathetic and motor systems could account for the simultaneous modulations in vascular conductance and flexor reflexes observed in the current study.

A contrasting explanation for the observed association is a spinal cord motor system modulation via plasma catecholamines. Immediate elevations of plasma norepinephrine (NE) have been documented for both bladder tapping and cutaneous afferent stimulation in subjects post SCI (Mathias, et al., 1976, Zhou, et al., 1997). In addition, a correlation between basal plasma catecholamines levels and muscle spasms has been shown in human SCI (Levin, et al., 1980). The permanent impairment of the blood-spinal cord barrier for small molecules like NE following cord injury (Popovich, et al., 1996) could result in NE reaching the cord directly from the blood. NE in animal preparations has been shown to facilitate spasms at low doses through facilitation of persistent inward currents (PICs) in motoneurons (Li, et al., 2004). These PICs underlie the plateau potentials that result in windup (Li and Bennett, 2003) and they have been implicated in spasticity syndrome following SCI (for review see(Heckman, et al., 2005). At the same time, spasms can be inhibited by high doses of NE through action on dorsal horn neurons and EPSPs (Li, et al., 2004). This function of NE is part of the normal descending inhibition of noxious afferent input via endogenous opioid-

containing interneurons (Kang, et al., 1998, Liu, et al., 1999, Lo, et al., 2003). Although descending tracts are lost in complete SCI, application of an α -2 adrenoceptor agonist has been shown to facilitate this endogenous opioid inhibition in spinal rabbits (Lo, et al., 2003).

The dual role of NE could explain our findings of a depressed noxious-triggered flexor reflex while providing a rationale for increased spontaneous flexor spasms observed elsewhere (Pedersen, et al., 1986, Riddoch, 1917). Early in the stimulation period, the levels might be low enough to show an initial potentiation, as was seen in a few subjects. The concentration of NE likely increased during the period of stimulation, which could have resulted in the depression of the flexor reflex observed in this study, consistent with the response of NE at different levels in the rat sacral spinal cord (Li et al. 2004). Further study of blood NE levels and the impact of sympathetic activity on stretch reflexes and other multijoint reflexes in SCI may help shed light on this matter.

Summary and Conclusions

Despite the general association of AD with increases in spasms, activation of sympathetic reflexes in this study were correlated with a significant decrease in the flexor reflex response to noxious afferent stimuli and possible motor-sympathetic links are discussed. Although the mechanism of a sympathetic-motor interaction cannot be established from the current study, the data are consistent with inhibition early in the flexor reflex pathways, resulting in a decrease in the total reflex output. While only spinal cord injuries at T5 and above are at risk for AD, it should be noted that lower level injuries are also susceptible to powerful autonomic reflexes in response to afferent stimuli from below the level of injury. Similar elevations in plasma catecholamine to bladder percussion (Zhou, et al., 1997) and lower extremity vasoconstriction to noxious cutaneous stimulation (Garrison, et al., 2008) have been reported. The results of this study bring attention to the possible interaction of motor and sympathetic reflexes in SCI above and below the T5 spinal level, and have implications for clinicians providing spasticity management and researchers investigating motor reflexes post SCI.

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Footnotes

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