Title: Riluzole decreases flexion withdrawal reflex but not voluntary ankle torque in human chronic spinal cord injury

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Running head: Riluzole and hyperreflexia in chronic SCI

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The objectives of this study were to probe the contribution of spinal neuron persistent sodium conductances to reflex hyper-excitability in human chronic spinal cord injury. The intrinsic excitability of spinal neurons provides a novel target for medical intervention. Studies in animal models have shown that persistent inward currents, such as persistent sodium currents, profoundly influence neuronal excitability, and recovery of persistent inward currents in spinal neurons of animals with spinal cord injury routinely coincides with the appearance of spastic reflexes. Pharmacologically, this neuronal excitability can be decreased by agents that reduce persistent inward currents, such as the selective persistent sodium current inhibitor riluzole. We were able to recruit seven subjects with chronic incomplete spinal cord injury who were not concurrently taking antispasticity medications into the study. Reflex responses (flexion-withdrawal and H-reflexes) and volitional strength (isometric maximum voluntary contractions) were tested at the ankle before and after placebo-controlled, double-blinded oral administration of 50mg riluzole. Riluzole significantly decreased the peak ankle dorsiflexion torque component of the flexion-withdrawal reflex. Peak maximum voluntary torque in both dorsi- and plantarflexion directions was not significantly changed. Average dorsiflexion torque sustained during the five-second isometric maximum voluntary contraction, however, increased significantly. There was no effect, however, on the monosynaptic plantar- and dorsi-flexor H-reflex responses. Overall, these results demonstrate a contribution of persistent sodium conductances to polysynaptic reflex excitability in human chronic spinal cord injury without a significant role in maximum strength production. These results suggest that intrinsic spinal cellular excitability could be a target for managing chronic spinal cord injury hyperreflexia impairments without causing a significant loss in volitional strength.
KEYWORDS

persistent sodium, interneuron, motoneuron
INTRODUCTION

Hyperactive reflexes and loss of motor control are common impairments experienced by individuals with chronic spinal cord injury (SCI). Though not thoroughly understood, these impairments are associated with the loss of descending cortical drive, as well as disruption of descending excitatory and inhibitory input from other supraspinal structures. Current USA Federal Drug Administration (FDA) approved pharmacological treatments for spasticity (i.e. hyperactive reflexes) act to either suppress excitatory, e.g. glutamatergic, synaptic transmission, facilitate inhibitory neuromodulation of spinal neurons (by noradrenergic $\alpha_2$ receptors), or facilitate inhibitory transmission to neurons in the spinal cord (via glycine or GABA) (Gracies et al. 1997). Although largely unexplored, another possible target of pharmacological intervention could be the intrinsic excitability of spinal neurons themselves. Before these treatment options can be implemented, however, the contribution of intrinsic cellular excitability (via ionic conductances) to reflex excitability and motor control impairments in human chronic SCI needs to be systematically investigated.

Studies of intrinsic electrical properties of spinal neurons in animal models of SCI have revealed dramatic differences in cellular excitability between the acute and chronic phases of injury. Acutely, interneurons, especially in the dorsal horn, become hyperexcitable, while motoneuron excitability decreases (Hounsgaard et al. 1988; Miller et al. 1996). Over time, however, motoneurons regain the ability to produce sustained output to synaptic input (Li and Bennett 2003; Li et al. 2004). Spasticity, measured using flexion reflexes in response to cutaneous stimuli, in these animal models routinely develops over the same time course as the recovery of this cellular excitability, driven by the return of specific ionic conductances, i.e. persistent inward currents (PICs) (Bennett et al. 2001; Li et al. 2004).
PICs in spinal neurons are voltage-gated (Crill 1996; Heckman et al. 2005; Heckman et al. 2008), amplify and prolong synaptic input (Prescott and De Koninck 2005), and underlie sustained output to sustained input, plateau potentials, and bistable behavior (Heckman et al. 2005; Hounsgaard et al. 1984; Lee and Heckman 1998). In particular, persistent sodium (NaP) conductances are essential for the production of rhythmic firing to sustained or slowly rising inputs, such as the action potential afterhyperpolarization (AHP) (Kuo et al. 2006; Lee and Heckman 2001; Theiss et al. 2007), and selectively reducing NaP decreases repetitive neuronal firing capabilities (Harvey et al. 2006b; Kuo et al. 2006; Kuo et al. 2005; Ptak et al. 2005; Theiss et al. 2007; Urbani and Belluzzi 2000). In animal models of SCI, NaP has been shown to be one of the key conductances driving prolonged reflexes and motoneuronal plateau potentials, and blocking these plateaus and currents blocks spastic reflexes (Li and Bennett 2003; Li et al. 2004).

Recent studies in humans have shown evidence that, like in animal models, PICs may also contribute to prolonged and amplified reflex responses in chronic SCI. For example, tests of lower-limb flexion-withdrawal reflex ‘wind-up’ (i.e. progressively increasing responses to repeated, identical amplitude stimuli) produce long-lasting, hyper-excitable reflex responses that may reflect the presence of plateau potentials in motoneurons, interneurons, or both (Hornby et al. 2003). Schmit and Benz (Schmit and Benz 2002) demonstrated that a brief stretch of hip flexors in subjects with chronic SCI produce long-lasting, heteronymous, multi-joint extensor spasms that likely activate an abnormally excitable interneuronal pathway. Paired motor unit studies have also suggested that intrinsic motoneuronal PICs likely drive involuntary spasms (Gorassini et al. 2004). In addition, Norton et al (Norton et al. 2008) demonstrated that a brief cutaneomuscular stimulus produces a short-lasting motor unit firing response in spinally intact control subjects, but a much longer-lasting response in subjects with chronic SCI, and attributed
this response prolongation to motoneuronal PICs. Taken together, the results from these human
studies reflect what is known about PICs from animal studies: PICs underlie plateau-potentials,
repetitive and self-sustained firing, and amplification and prolongation of synaptic input.

The objectives of this study were: 1) to pharmacologically probe the contribution of
intrinsic neuronal conductances to reflex excitability and voluntary motor control by reducing
persistent sodium currents with riluzole, and 2) to determine the spinal locus of hyperexcitability,
i.e. interneurons, motoneurons, or both. In particular, we chose to assess the impact of persistent
sodium currents on the polysynaptic flexion-withdrawal reflex response, to the mono-synaptic
electrically-elicited H-reflexes, and to voluntarily produced maximal contractions in the lower
limb (about the ankle) in subjects with chronic incomplete SCI. Riluzole has recently been
shown to decrease spastic flexion reflexes in response to noxious and non-noxious cutaneous
stimuli in spinal cord injured rats (Kitzman 2009). Our results support this finding and suggest
that NaP does indeed have a strong effect on the amplitude of polysynaptic reflex responses,
especially at the interneuronal level, and that the intrinsic excitability of spinal neurons could
provide a novel and effective pharmacological target for the medical management of
hyperreflexia and motor impairments in human chronic SCI.

Portions of this work have been presented previously in abstract form (Theiss et al.
2008).

MATERIALS AND METHODS

General Experimental Procedures

All studies and procedures were conducted in accordance with the Declaration of
Helsinki and with the full approval of the Northwestern University Office for the Protection of
Research Subjects (OPRS) Institutional Review Board (IRB) in compliance with their guidelines for research involving human subjects. Informed consent was obtained in writing from all subjects before enrollment and participation in the research study. All studies were conducted in research laboratories at the Rehabilitation Institute of Chicago (RIC, Chicago, IL, USA).

Briefly, the study design involved a double-blinded, single-dose, placebo-controlled oral administration of 50mg riluzole (Rilutek®, sanofi-aventis U.S., Bridgewater, NJ, USA) given after the completion of the pre-test experimental protocol. After approximately a 90 minute wait (the approximate time to peak plasma concentration), a post-test repeating the same experimental protocol as the pre-test was conducted. Both the pre-test and post-test sessions were completed on the same experiment day. At least seven days for a “washout” period were provided between experiment days. The riluzole and the placebo administration order was randomized, blinded by enclosure in identical-looking capsules, and packaged into “Experimental Day A” and “Experimental Day B” prescription bottles with sequential numbering by the RIC Pharmacy.

Neither the subject nor the study staff knew which drug was being administered on which day, though the blinding code could be broken by pharmacy staff in case of a medical emergency.

Subject population

A total of seven subjects with chronic (>1yr) motor-incomplete SCI participated in both drug and placebo testing days of this study. As shown in Table 1, 2/7 subjects were classified as AIS C, 4/7 subjects were classified as AIS D, and 1/7 subjects were assessed as between AIS C-D. Six of the subjects had not been taking anti-spasticity medications for more than one year prior to enrollment in the study, and one of the subjects had not taken anti-spasticity medication for more than 14 days before participating in the first experiment day. Clinical evaluation of
strength and spasticity were performed before transferring subjects into the experimental apparatus, approximately 30-45 minutes before beginning quantitative testing. These clinical measures were assessed using the American Spinal Injury Association (ASIA) Impairment Scale classification (Marino et al. 2003), Modified Ashworth Scores (knee extensors/knee flexors, 0-4 scale, 0: no impairment, 4: severe spasticity, and the Spinal Cord Assessment Tool for Spasticity (Benz et al. 2005, SCATS, extension/flexion/clonus, scale of 0-3, 0: no impairment, 3: severe spasms lasting longer than 10 seconds). A summary of the subjects’ clinical features are presented in Table 1. Specific inclusion/exclusion criteria for participation included: non-progressive lesion between C1-T10; below T10 excluded due to potential peripheral nerve damage/cauda equina injury. Subjects were medically stable, with no concurrent medical illnesses, were not concurrently taking medications for spasticity or pain, and had medical clearance from their primary internists or physiatrists to participate. Subjects were also excluded for significant cardiorespiratory, metabolic, orthopedic, or other neurological disease. Women of childbearing potential were not excluded, although women who were pregnant or nursing were excluded due to unknown or potential risks from the pharmacological agent to the fetus or nursing child. As determined by the subject’s primary physician or physiatrist, subjects were also excluded if there were any potential interactions of riluzole with other concurrent medications or if the subjects had a history of sensitivity to the test agents or their components.

Testing apparatus and evaluation of spastic reflexes and motor impairments

Measurements of electromyogram (EMG) activity and joint torques were used to quantify stimuli-evoked reflex responses and volitional motor strength. As previously described (Hornby et al. 2006; Hornby et al. 2003) and shown in Figure 1, subjects were seated in an adjustable
chair with their test foot securely strapped to an instrumented footplate mounted on a six degree
of freedom (DOF) load cell (ATI, Apex, NC, USA) attached to a mechanical fixture (Biodex
Rehabilitation System 3, Biodex Medical Systems Inc., Shirley, NY, USA). Surface EMG
electrodes (Delsys, Boston, MA, USA) were attached to the skin above the muscle to measure
the activity in the tibialis anterior (TA), soleus (SOL), medial gastrocnemius (MG), vastus
lateralis or medialis (VL/VM), rectus femoris (RF), and medial or lateral semimembranosus/
semitendinosus (MH/LH) muscles. EMG signals were amplified (x1000) and filtered (20-250Hz)
online before acquisition. Endpoint torque signals were low-pass filtered (200Hz). Customized
LabVIEW (National Instruments, Austin, TX, USA) software was used for data acquisition
(sampled at 1000Hz) and control of electrical stimuli. Lower-limb segment lengths and endpoint
torques were used to calculate ankle, knee and hip joint torques (Schmit et al. 2000).

Quantitative assessment of reflex excitability and voluntary motor strength:
Torque and EMG measurements of the flexion withdrawal reflex response were used to
assess reflex excitability. Flexion withdrawal reflexes were elicited by a controlled electrical
stimulus train (biphasic, train of 10 - 1ms pulses, 200Hz, for 50ms) delivered through a pair of
bipolar electrodes placed 0.5-1cm apart on the medial plantar arch of the foot. Flexion reflex
‘threshold’ was determined by the smallest amplitude stimuli to produce a TA EMG response
and at least 1 Nm of dorsiflexion torque in two of three stimulus trains given 20 seconds apart.
The threshold stimulus intensity was determined at the beginning of each testing session.
Flexion reflex responses to three stimulus trains at 20 second intervals were tested at 1, 2, 3, 4,
and 5 times the threshold to assess the response (EMG or torque) versus stimulus intensity
(stimulus-response) relation. Generally, most subjects perceived this stimulus as noxious.
H-reflex and M-wave EMG responses were elicited via a bipolar stimulating electrode with two 1 cm diameter contacts located 3 cm apart from their centers to assess monosynaptic reflex responses and for normalizing TA and SOL EMG responses. Responses for plantarflexion were elicited by stimulation of the tibial nerve at the popliteal fossa, and responses for dorsiflexion were elicited by stimulation of the common peroneal nerve branch just lateral to the head of the fibula. H-reflex and M-wave responses were measured by determining the H-reflex threshold and increasing the stimulus intensity in 1-2mA increments until the M-wave amplitude no longer increased. (For additional certainty, the stimulus intensity was increased by 20% after this point for a supra-maximal measurement.) Stimuli were delivered every 5 seconds. The maximal H-reflex and M-wave responses allowed for comparison of H-reflex maximum amplitude and M-wave maximum amplitude (Hmax/Mmax) ratios across subjects during different recording conditions. TA and SOL EMG responses were normalized to the amplitude of the maximal M-waves (Mmax).

Torque and EMG responses to maximum voluntary contractions (MVC) were also measured for assessment of subject ankle strength. With the knee extended, measurements of the volitional strength of the plantarflexors were made from an ankle position of 0° (neutral), and measurements of the volitional strength of the dorsiflexors were measured from an ankle position of 30° plantarflexion. Three trials each of maximal voluntary dorsiflexion and three trials of maximal voluntary plantarflexion were performed upon verbal cue. Subjects were verbally instructed and motivated to maintain these maximum contractions for approximately five seconds. Visual feedback of torque production was not provided, though subjects were generally consistent in their MVC torques. Peak MVC torque responses, duration about the peak, and average sustained torque produced during the MVC were measured and averaged over the three
trials. To account for any differences in MVC duration due to instruction or reaction time variations from subject to subject, measurements involving torque over time were normalized to instruction duration and reported in relation to time in seconds.

Pharmacological administration

To control for diurnal fluctuations in reflex behavior and for subjective effects of agent administration, these studies were performed using a double-blinded, placebo-controlled, randomized design. Either a placebo or 50mg riluzole (Rilutek®) was administered following the pre-test quantitative evaluation. After a wait period of approximately 90mins, the post-test was performed. (Note: post-test clinical evaluations were performed before transferring the subject into the experimental set-up, approximately 45-60mins after riluzole administration. Since these clinical tests were performed approximately 30-45min before the time to peak plasma concentration of riluzole, it is unknown if an effective concentration of the drug had been reached by the time of these evaluations.) For each subject, pre-tests were performed at approximately the same time in the morning, and post-tests were started at approximately the same time in the afternoon. During the post-test, the subjects repeated the entire protocol using a similar experimental paradigm and set-up (subject positioning, electrode placement) as in the pre-test. A drug “washout” period of at least seven days was taken between testing days.

Data analysis

Data were analyzed off-line using custom-written analysis scripts in Matlab (Mathworks, Natick, MA, USA). As stated above, all data had been collected at a sampling frequency of 1000Hz. Torque measurements were smoothed by a 10 point moving window average, utilizing
the Matlab `filtfilt` function (a zero-phase delay filter) as an all zero, finite impulse response (FIR) filter resulting in an effective cutoff frequency of 25Hz. EMG signals were rectified and low-pass filtered at 40Hz (using a 2\textsuperscript{nd} order Butterworth filter and the `filtfilt` function in Matlab) for peak amplitude and duration calculations. Peak, onset latency, and duration of the dorsiflexion torque responses to the flexion withdrawal stimuli were calculated from the filtered data, and the results from the three stimulus trains were averaged. Peak torque response was measured as the maximum torque for each stimulus train. Onset latency was measured from the beginning of the stimulus train to the first point on the torque response to cross a threshold of the mean plus three standard deviations (+3sd) of the baseline torque measurement from the first 50ms of each trial. The duration was calculated as the time between the onset of the response and the end of the response, defined as the point where the torque dropped below the threshold of mean + 3sd of the baseline. Peak, onset latency, and duration of the normalized and the lowpass filtered TA and SOL EMG responses were calculated in the same manner as the torque responses. The area of the normalized, filtered EMG responses was calculated using the Matlab `trapz` function, estimating the integral of each EMG response from the calculated response onset to the calculated response end (through the response duration).

Strength measurements in both dorsiflexion and plantar flexion were assessed from the MVC protocol. Peak torque was measured as the maximum torque (in Nm) produced in the instructed direction, and average sustained torque was measured as the area under the torque curve during the instruction period, normalized to instruction duration, and reported in relation to time in seconds (in Nm*s/s).

Statistical analysis
Results from the experimental protocol were compared between pre-test and post-test, and results from drug administration were expressed in relation to placebo administration. (By performing pre-tests and post-tests, subjects served as their own controls, and expression of double-blinded results in relation to placebo administration assessed the changes due specifically to riluzole administration.) Significance was determined by 2-way repeated measures ANOVA and Student’s t-tests. Levels of significance were set at p < 0.05 unless otherwise indicated.

RESULTS

The contribution of spinal neuronal NaP to hyper-excitable flexion withdrawal reflexes and voluntary strength was investigated in seven subjects with chronic incomplete SCI in a double-blind, placebo controlled study design using a single-dose oral administration of 50mg riluzole (Rilutek®) as a pharmacological probe. Our results demonstrate that NaP in chronic, incomplete SCI contributes to the stimulus threshold for the flexion-withdrawal response, the amplitude of the flexion withdrawal response, and the average sustained voluntary torque. NaP does not appear to have any effect on electrically elicited monosynaptic H-reflexes, however. These results suggest that the hyperexcitability in the dorsiflexion component of the polysynaptic flexion withdrawal response is related to NaP in spinal interneurons.

Following riluzole administration, the threshold stimulus intensity for the flexion withdrawal response significantly increased compared to placebo administration (Figure 2, p = 0.03, n = 7; riluzole: post-test minus pre-test = 2.0 ± 2.0mA (mean ± sd); placebo: post-test minus pre-test = 0.3 ± 2.6 mA (mean ± sd)). Pre-test threshold values for placebo and riluzole conditions were not significantly different (p = 0.4, paired Students’ t-test, n = 7).
Compared with placebo, riluzole administration produced a significant decrease in the peak amplitude of the ankle dorsiflexion torque component of the flexion withdrawal reflex, as shown in the example in Figure 3. This decrease occurred over the series of stimulus intensities producing a significant difference in the stimulus-response relation with respect to placebo (post-test minus pre-test difference, 2-way ANOVA with replication: \( p = 0.0003, F = 14.9, n = 7 \), Figure 4A; post-test to pre-test percent change, 2-way ANOVA with replication: \( p = 0.002, F = 10.2, n = 7 \), Figure 4B). At each stimulus intensity, peak torque amplitude decreased approximately 20% (Figure 4B). Torque response latency, duration, and area did not significantly change in post minus pre values after riluzole administration with respect to placebo, although there was a significant percent change in torque response duration (2-way ANOVA with replication, percent change: \( p = 0.03, F = 5.2, n = 7 \)). This change reflected an overall increase in response duration (averaged over all stimulus intensities) following placebo administration (post-pre difference = 284 ms ± 861 ms (mean ± sd); percent change of 28.7% ± 62.2% (mean ± sd), \( n = 7 \)) and less of an increase in duration following riluzole administration (post-pre difference = 13 ms ± 396 ms (mean ± sd); percent change of 1.1% ± 31.7% (mean ± sd), \( n = 7 \)). Tibialis anterior (TA) EMG responses were consistent with the above results but not significant.

After riluzole administration, threshold stimulus intensity increased and peak torque response decreased, changing the input-output (i.e. stimulus intensity - torque amplitude response) profile for the flexion withdrawal reflex (Figure 5). Following placebo administration (Figure 5A), the pre (filled circles, solid line) and post (open circles, dashed line) input-output relations almost overlapped. With riluzole administration (Figure 5B), however, the post (open triangles, dashed line) input-output relation shows a shift to the right and a decrease in the initial
response slope (regression line fit to first three points) when compared to the pre (filled triangles, solid line) relation. This initial slope decreased significantly following riluzole administration (29%, \( p = 0.015 \), \( n = 7 \), paired t-test), but did not decrease significantly following placebo administration (15%, \( p = 0.07 \), \( n = 7 \), paired t-test). As seen in Figures 4B and 5A, the slope of the stimulus response relationship for the placebo decreased only because the response to the 1X threshold stimulus intensity increased by 78% while the response to the 2X and 3X threshold changed very little (1% increase and 1% decrease, respectively). This stimulus threshold increase and slope decrease is consistent with \textit{in vitro} reports that riluzole produces a rightward bias shift and gain decrease in the input-output relation in animal spinal neurons (Kuo et al. 2006; Theiss et al. 2007).

To assess the effects of riluzole on voluntary strength, subjects were instructed to produce maximum voluntary contractions (MVCs) in either dorsiflexion (DF) (at 30° of plantarflexion) or plantarflexion (PF) (at neutral ankle position) directions for approximately five seconds with verbal encouragement. The knee was fully extended in both situations. Overall, the subjects produced a pre-test range of 2.6 to 21.6 Nm of peak DF torque (pre-placebo: 14.5 ± 6.3 Nm; pre-riluzole: 13.4 ± 6.7 Nm; mean ± sd) and a pre-test range of 5.6 to 54.5 Nm of peak PF torque (pre-placebo: 31.9 ± 15.6 Nm; pre-riluzole: 33.8 ± 16.4 Nm; mean ± sd). Pre-test peak DF and PF torque values were not significantly different between the placebo and riluzole conditions (pre DF: \( p = 0.69 \); pre PF: \( p = 0.13 \); paired Student’s t-test, \( n = 7 \)). Following riluzole administration, the pre- to post-test difference for DF peak torque was significant between the placebo and riluzole conditions (Figure 6A), because after placebo administration, DF peak torque decreased significantly (\( p = 0.02 \), \( n = 7 \)) from pre to post administration (pre: 14.5 ± 6.3Nm; post: 13.0 ± 6.0Nm). Following riluzole administration, however, DF peak torque did
not significantly change (p = 0.79; pre: 14.2 ± 6.4Nm; post: 14.3 ± 7.0Nm). The decrease in peak torque in the placebo condition, but no change after riluzole administration resulted in a significant difference between the two conditions in both the absolute change (post-test minus pre-test, p = 0.03, n = 7) and the percent change (p = 0.01, n = 7). Conversely, peak PF torque did not significantly change in either condition (Figure 6B).

Unexpectedly, although riluzole did not change the peak DF torque from pre-test to post-test (note that peak DF torque decreased following placebo administration, however), the percent change in average sustained torque (normalized to command duration in Nms/s, see Methods) increased significantly with riluzole administration when compared with placebo (riluzole: 28% ± 34%; placebo: -12% ± 29%, p = 0.04). An exemplary illustration of this increase is shown in Figure 7. Though peak DF torque did not significantly change after riluzole administration, the total torque produced during the MVC increased (Figure 7A, top). For this subject, this change following riluzole administration may be related to the change in EMG activity (Figure 7A, bottom), as the TA EMG is prolonged through the command (between the vertical hash-marked lines), while the co-contraction, represented by MG activity, was not present during the MVC in the post-test recording. Co-contraction between TA and MG (and sometimes Sol) during DF MVCs was observed in 5/7 subjects, and MG activity in all five of these subjects was reduced following riluzole administration. Neither the average sustained PF torque nor other features of the PF MVC, however, significantly changed in either placebo or riluzole conditions (Figure 7B).

The change in average sustained DF torque was also significantly related to initial voluntary DF strength. As shown in Figure 8, the percent change in average sustained DF torque was negatively correlated to the pre-test peak DF isometric MVC torque after riluzole
administration (gray dashed line, $r^2 = 0.86$, repeated measures ANOVA, $F = 30.4$, $p = 0.003$) but not after placebo administration (solid black line, $r^2 = 0.0006$, repeated measures ANOVA, $F = 0.0003$, $p = 0.99$). This relationship indicates that the weaker subjects with the lowest initial voluntary DF isometric MVC torque exhibited the greatest increases in average sustained DF isometric MVC torque following riluzole administration, while the stronger subjects showed less of an increase in average sustained DF torque.

The percent decrease in flexion-reflex peak DF torque after riluzole administration was also related to initial voluntary DF strength. As shown in Figure 9, the percent change in peak flexion reflex DF torque was positively correlated to the pre-test peak DF torque after riluzole administration (Figure 9B) for 3X threshold (open triangles, solid black line, $r^2 = 0.84$, $p = 0.003$), 4X threshold (open squares, dashed black line, $r^2 = 0.69$, $p = 0.02$), and 5X threshold (open circles, dotted black line, $r^2 = 0.74$, $p = 0.01$). Riluzole had the greatest relative effect on the peak flexion-reflex torque of the weaker subjects, and less of a decrease for the stronger subjects. No relationship between change in reflex torque and initial strength was seen after placebo administration (Figure 9A).

H-reflexes and M-waves were also tested in each subject for the TA and SOL. TA H-reflexes were able to be elicited in 6 of 7 subjects, and SOL H-reflexes were present in all 7 subjects. The peak-to-peak amplitude for the maximum H-reflex amplitude was compared to the peak-to-peak amplitude of the maximum M-wave amplitude (Hmax/Mmax ratio). For both the TA and the SOL, Hmax/Mmax ratios were not significantly different pre- to post-test in either the placebo (TA: $p = 0.83$, $n = 6$; SOL: $p = 0.86$, $n = 7$) or riluzole (TA: $p = 0.85$, $n = 6$; SOL: $p = 0.35$, $n = 7$) conditions.
Pre-test to post-test changes in clinical measures of spasticity (Modified Ashworth scores and SCATS) were minimal and not significantly different between placebo and riluzole administration. (Note: as mentioned in Methods, clinical evaluations were performed before transferring the subject to the experimental apparatus, approximately 30-45min before the time to peak plasma concentration of riluzole. Thus, these changes are difficult to interpret.)

**DISCUSSION**

This study examined the contribution of intrinsic neuronal excitability, via persistent sodium currents, to reflex activity, volitional strength, and motor discoordination in chronic (>1yr) incomplete SCI. The effects of riluzole administration on flexion withdrawal reflex responses and voluntary strength were assessed in seven subjects with chronic incomplete SCI using a double-blinded, placebo-controlled study design. The major results from this study demonstrated that, when compared to placebo administration, riluzole significantly decreased the peak DF torque component of the flexion withdrawal reflex response and significantly increased average sustained isometric DF torque maintained during five-second MVC trials that, in five of the seven subjects, was related to a decrease in antagonist co-contraction. In addition, changes in both flexion withdrawal response peak DF torque and MVC average sustained DF torque strongly correlated to initial isometric DF strength (as assessed by MVC peak torque). TA and SOL Hmax/Mmax ratios were not significantly different in either the placebo or riluzole conditions. As discussed below, these results suggest that persistent sodium conductances at the interneuronal level greatly contribute to polysynaptic reflex excitability in chronic SCI.

*Contribution of persistent sodium conductances to reflex excitability and motor control*
The first objective of this study was to pharmacologically probe the contribution of intrinsic neuronal conductances to reflex excitability and voluntary motor control by reducing persistent sodium currents with riluzole administration. In cellular electrophysiology, riluzole is known to be a specific, progressive inhibitor of the NaP current (Ptak et al. 2005; Urbani and Belluzzi 2000). This NaP current is essential for producing sustained, repetitive output (rhythmic firing) to sustained or slowly rising inputs (Kuo et al. 2006; Lee and Heckman 2001; Theiss et al. 2007). Decreasing NaP decreases repetitive-firing capabilities, reduces input-output gain, and increases input-initiated response threshold (Harvey et al. 2006b; Kuo et al. 2006; Kuo et al. 2005; Ptak et al. 2005; Theiss et al. 2007; Urbani and Belluzzi 2000). The effects of riluzole administration on the flexion-withdrawal response in our subject sample mimicked the increased threshold and gain reduction changes in the cellular input-output relation produced by reducing NaP. As riluzole affects cellular excitability by inhibiting the sodium PIC, it is possible that riluzole inhibits NaP in human spinal neurons as well, and that NaP may be a major contributor to hyperexcitable reflex responses and muscle activation discoordination in human, chronic incomplete SCI.

In the drug-prescribing literature, riluzole is often listed also as an anti-glutamatergic agent. However, a thorough review by Pittenger et al (Pittenger et al. 2008) revealed that many of the additional molecular effects attributed to riluzole have been obtained in vitro at concentrations that are much higher than would be therapeutically achievable. A riluzole dose of 50mg b.i.d produces a plasma concentration of approximately 0.9-1.6μM (Lacomblez et al. 1996) and the estimated average concentration in ALS patients receiving riluzole treatment is 1μM (Urbani and Belluzzi 2000). Though we cannot completely rule out the possibility of anti-glutamatergic activity, we would have expected to see decreases in every motor response that
relies on glutamate for synaptic transmission (e.g. responses relayed by excitatory afferents including flexion withdrawal responses and H-reflexes, voluntary activation of motoneurons, etc.) if this was the primary mechanism of riluzole action.

Spinal locus of riluzole activity and reflex hyperexcitability

The second objective of this study was to determine the spinal locus of hyperexcitability, i.e. interneurons, motoneurons, or both. In animal studies, riluzole has been shown to reduce NaP and decrease cellular excitability in both spinal motoneurons (Kuo et al. 2006) and interneurons (Theiss et al. 2007). All of our experimental protocol (flexion-withdrawal, MVCs, H-reflexes) tested motoneuron excitability, at least to some degree. Interneuronal excitability was primarily evaluated by testing the flexion-withdrawal reflex which involves polysynaptic interneuronal pathways. Additionally, MVCs also allowed for examination of preserved corticospinal activity. The decrease in the polysynaptic flexion withdrawal reflex response without decreases in peak MVC torque or relative amplitude of H-reflexes, strongly suggests that in this study of subjects with incomplete SCI, decreasing NaP by riluzole has the strongest effect on spinal interneurons. The result that riluzole did not decrease the amplitude of peak MVC torque was unexpected, since NaP has a profound effect on motoneuron excitability in animal studies. An additional unexpected result was that average sustained DF MVC torque significantly increased after riluzole administration when compared to placebo. In five of our seven subjects (see example in Figure 7), this was accompanied by, and possibly attributable to, a decrease in antagonist co-contraction, a significant factor in motor discoordination which might have interneuron involvement. It is possible that the decrease in TA EMG accompanied by the increase in PF muscle EMG seen in these subjects was mediated by classic autogenic inhibition
from Ib/Golgi tendon organ spinal input. The underlying function of this inhibition of homonymous muscle activity with facilitation of antagonist muscle activity involves group I non-reciprocal interneurons that receive predominant input from both group Ia and group Ib afferents (Jankowska 2001). In our study, all MVCs were isometric with a fixed ankle angle (thus Ia muscle spindle activation was minimal), and the foot was secured by dorsum straps to the footplate (thus providing additional tonic cutaneous input during DF MVCs). Cutaneous input has been shown to enhance the input from group Ib afferents (Powers and Binder 1985) to spinal neurons, so it is possible that in our experimental set-up, Ib input to already highly excitable group I interneurons was additionally facilitated. A presumably disynaptic reciprocal facilitation of ankle PF muscles by ankle DF muscles has also been previously reported in subjects with spasticity after SCI and hemiplegia after stroke (Crone et al. 2003). The decrease in co-contraction following riluzole administration, then, may also be the result of the decrease in spinal interneuron excitation.

The stronger action of riluzole on polysynaptic reflex pathways but not on direct motoneuron excitability (e.g. peak MVC) may also point to a difference in the relative impact of NaP amplitude to interneuron versus motoneurons excitability, or a difference in sensitivity to riluzole in these neurons. Previous work has shown that spinal neurons, interneurons especially, exhibit varying amounts of NaP which is directly correlated to their repetitive firing capabilities: cells with larger amplitude NaP have strong repetitive firing, while cells with little NaP only respond with a few action potentials regardless of the duration of the input (Theiss et al. 2007). It is possible that human spinal interneurons may be more reliant on NaP PICs for sustained output excitability and that decreasing NaP with riluzole would then have a more profound and noticeable effect in these cells. Interneurons may also simply be more sensitive to riluzole than
motoneurons. For example, in respiratory pacemaking, some cells have been shown to be more sensitive to riluzole than others, suggesting a larger reliance on NaP for firing output, while others might be more reliant on CaP for their rhythmic activity (Pena et al. 2004).

Voluntary strength related effects of riluzole and implications for SCI

In this study, the relative effect of riluzole was strongly correlated to lower limb volitional strength. Lower limb strength may provide an inference to the extent of the spinal injury, although contributing factors such as muscle mass prior to injury, time since injury, and amount of atrophy may confound this assumption. Our subjects had intact peripheral nerves, so atrophy from denervation was likely minimal. Presumably, less paralysis would result in less atrophy. If anything, atrophy or greater percent decrease in muscle mass would only broaden the range of strength and no detract from this relationship. In subjects with less preserved volitional strength (lower peak MVC DF torque), a greater decrease in the DF component of the flexion withdrawal response and a greater increase in the average sustained MVC DF torque was a profound finding. This result may demonstrate a relationship between cellular hyperexcitability and the amount of preserved descending input, or the “completeness” of the injury. For example, in subjects with less preserved pathways (e.g. less voluntary strength), riluzole had a greater relative effect on the DF torque amplitude during the flexion withdrawal reflex response, whereas in subjects with more preserved pathways (e.g. greater voluntary strength), riluzole had a smaller relative effect. Further investigation is necessary to determine if this effect would generalize to other joints. It is possible, as described above, that in more complete injuries interneurons may rely more heavily on NaP for processing synaptic input and producing repetitive firing output. Additionally, it also possible that there is more NaP in cells with less
preserved descending input as a result of an adaptation to the lack of this synaptic or
neuromodulatory input. For example, recent studies have shown that PICs in chronic SCI
models become supersensitive to serotonin (Harvey et al. 2006a; Li et al. 2007) and
norepinephrine (Rank et al. 2007). In more complete injuries, it is possible that cells with an
increase in the loss of descending input compensate more with a higher degree of
supersensitivity adaptation. Riluzole, then, is not necessarily taking the place of descending
input, but instead is providing a decrease in the adapted cellular excitability. Consistent with
animal studies, decreasing NaP amplitude could decrease the amplification and prolongation of
the synaptic input (Prescott and De Koninck 2005), increase neuronal input threshold for the
onset of repetitive discharge, and decrease the discharge frequency for any given input,
effectively decreasing input-output gain (Kuo et al. 2006; Theiss et al. 2007). Thus, riluzole is
not acting as a descending inhibitor or a neuromodulator, but is acting on the end result of
modulation or disinhibition, i.e. the activation and strength of intrinsic PICs (Heckman et al.
2008).

The implications of the effect size relating to pre-drug strength are that pharmacological
interventions targeting intrinsic excitability may have greater effectiveness to reduce
hyperexcitability in weaker individuals. In addition, riluzole did not decrease DF or PF
maximum voluntary strength measures in our study, suggesting a possible reduction in a
potentially problematic reflex without the loss of strength often associated with other anti-
spasticity medications. As for the potential for reducing spasticity in chronic SCI by decreasing
intrinsic neuronal excitability, our results suggest that hyperexcitable, polysynaptic reflexes can
be decreased by a drug that reduces intrinsic neuronal excitability through NaP. This opens up a
novel target for the alleviation of spastic reflexes, separate from providing central inhibition (e.g. by baclofen) or inhibitory neuromodulation (e.g. by tizanidine).

Limitations

Limitations of this study included sample size, heterogeneity of subject sample, short-term versus long-term effects of riluzole administration, and functional consequences. The primary limiting factor for the subject sample size in this study was the difficulty in recruiting subjects that were not restricted by the exclusionary criteria of concurrent use of anti-spasticity or pain medications. For this study, only subjects who were not taking anti-spasticity or other centrally acting medications (e.g. for the treatment of pain or depression) were recruited and qualified to participate. Despite the small number of subjects, however, the decrease in flexion withdrawal torque response was still significant. For individuals who experience larger and more troublesome spastic impairments that necessitate treatment by anti-spasticity and anti-pain medications, the effects of riluzole might be different, but we would expect that riluzole would significantly reduce hyperexcitable reflex responses in subjects with more severe spasticity as well, perhaps even to a greater extent. Even though the sample size was limited, the effects of riluzole were uniform across subjects. For example, in the flexion withdrawal response, riluzole increased the stimulus threshold current 9-50% in 6/7 subjects (in one subject, the threshold current decreased, though the decrease was less than with placebo, -12% with riluzole compared with -18% with placebo). Additionally, riluzole consistently decreased peak DF torque responses at 2-5X threshold in 6/7 (in one subject whose stimulus threshold increased, riluzole decreased peak DF torque responses in only 1, 4 and 5X threshold). Placebo administration, conversely, produced mixed changes: increases in peak DF torque responses between 1-250%, or
decreases of less than 20%. Overall, however, riluzole’s effect when compared to placebo was a greater increase in stimulus threshold and a greater decrease in peak DF torque response (with the exception of the single subjects as noted).

Another possible limitation was that our subject sample was heterogeneous displaying a range of AIS classifications, varying levels of lower limb clinical spasticity measures (e.g. Ashworth scores), and varying levels of voluntary ankle strength. Though not a homogenous group, this range did allow for comparison across the ranges of injury level, spasticity, and strength. Inter-subject comparisons demonstrated significant correlations between initial voluntary DF strength (peak isometric DF MVC torque) and increases in average sustained voluntary DF torque and also between initial voluntary DF strength and decreases in flexion-withdrawal DF torque responses following riluzole administration. Additionally, the fact that the overall results were significant despite the heterogeneity is in itself remarkable and may speak to the robustness of the effect.

It is possible that long-term effects of chronic riluzole administration would yield different results than what we report above. Additional studies would need to be done before utilizing this drug as part of a daily regimen to manage spasticity. Riluzole may be useful as an “as-needed” medication, but again, more studies would need to be done to test its efficacy in this capacity.

Finally, although we report a decrease in the ankle component of a polysynaptic reflex response without a decrease in volitional ankle strength, the functional effects of riluzole administration need further study. Questions about possible detriments to locomotion (e.g. toe clearance) are still open to investigation.
Even with these remaining questions, this study provides insights into the mechanisms and spinal locus of hyperexcitable polysynaptic reflexes in chronic SCI. Significant results were obtained even with a small sample size from a heterogeneous population, and further investigation based on these findings will shed light on the practical and appropriate use of drugs that target the intrinsic excitability of spinal interneurons to manage spasticity in chronic SCI.

Conclusions

This study is the first to show the effects of riluzole on hyperexcitable reflexes and strength in chronic human SCI. Overall, results from this study suggest that cellular excitability via persistent sodium conductances in spinal interneurons may contribute to hyperexcitable reflex responses and that cellular excitability is a potential target for the medical treatment of spasticity/hyperexcitable reflex responses. Riluzole may also present a tool to treat spasticity as an adjunct to physical therapeutic interventions. Using riluzole to control spasticity without a generalized reduction in strength may allow for additional benefit from locomotor training or other interventions to improve functionality. As previously suggested by Gracies et al (Gracies et al. 1997), intrinsic cellular excitability presents a novel target for pharmacological intervention, and impairments such as hyperactive reflexes and motor discoordination might be reduced by targeting intrinsic neuronal excitability, facilitating the potential to improve function for individuals with chronic SCI.

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DISCLOSURES

No conflicts of interest are declared by the authors.
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**Figure Legends**

**Figure 1:** The test apparatus for measuring isometric motor behavior. The test foot was secured to the Foot Plate which was attached to a six degree of freedom Load Cell. The Foot Plate and Load Cell were mounted on the rotational axis of the Biodex system Controller. Surface EMG Electrodes were affixed to the skin above several muscles to record muscle activity.

**Figure 2:** Riluzole significantly increased the amplitude of the threshold Stimulus Current (in mA, y-axis) required to elicit the minimum flexion withdrawal reflex response. Pre-test average values are indicated with solid fill bars, and Post-test average values are indicated with open fill bars. Drug conditions are indicated on the x-axis for Placebo (left) and Riluzole (right) administration.

**Figure 3:** Example of the effects of Placebo and Riluzole administration on flexion withdrawal reflex dorsiflexion Ankle Torque response amplitude (in Nm, y-axes). After Placebo administration (top trace), pre-test (black line) and post-test (gray line) Ankle Torque responses were similar for this subject. After Riluzole administration (bottom trace), the post-test (gray line) Ankle Torque response peak amplitude decreased in comparison to the pre-test (black line). Arrows below the x-axes indicate the time at which the Stimulus was applied. Traces have been truncated as shown by diagonal hash marks; the protocol interval between stimuli was 20s. Time, in seconds, is shown on the x-axis, with a 1s scale bar indicated.
Figure 4: Aggregate changes in flexion withdrawal reflex response to all stimulus intensities after Placebo or Riluzole administration. For both panels, the Placebo condition is indicated with black circles and black lines; the Riluzole condition is indicated with gray triangles and gray lines. Zero on the y-axes is indicated by a dotted line. Markers represent the sample mean, and error bars indicate 1 standard deviation. A) Riluzole administration decreased the peak flexion withdrawal reflex DF torque response at all stimulus intensities (x-axis, 1-5 times Stimulus Threshold). Significant differences (*) between Placebo and Riluzole in the post-test minus pre-test Mean DF Torque Difference (y-axis, in Nm) were seen at 3 and 4 times threshold. B) Riluzole administration decreased the peak flexion withdrawal reflex DF torque by approximately 20% at all stimulus intensities (x-axis, 1-5 times Stimulus Threshold). Significant differences (*) between Placebo and Riluzole Mean DF Torque % Change (y-axis) were seen at 4 and 5 times Stimulus Threshold. Note: the error bar for the Placebo 1-x Stimulus Threshold value has been truncated to show detail for the other stimulus intensities.

Figure 5: Input-output relation for the Peak DF Torque component of the flexion withdrawal response. For both panels, Pre-test values are indicated by filled markers and solid lines, and Post-test values are indicated by open markers and dashed lines. The group mean Peak DF Torque, in Nm, is shown on the y-axis, and the mean Stimulus Current Amplitude, in mA, is shown on the x-axis. Error bars indicate 1 standard deviation. A) The stimulus intensity v. Peak DF Torque response relation was similar in the Placebo Pre- (filled circles) and Placebo Post-test (open circles). B) Riluzole administration increased the average threshold stimulus amplitude and decreased the average Peak DF Torque response, shifting the stimulus intensity v. Peak DF Torque response relation to the right and decreasing the gain of the initial three points. Riluzole
Pre-test values are indicated with filled gray triangles and Riluzole Post-test values are shown by open gray triangles.

Figure 6: Riluzole administration did not significantly decrease Mean Peak Torque during maximal voluntary contractions. In both panels, Pre-test values are shown with solid-filled bars, and Post-test values are shown with open fill bars. Mean Peak Torque, in Nm, is shown on the y-axis, and the DRUG condition is shown on the x-axis. Error bars indicate 1 standard deviation. A) Maximum voluntary DF Mean Peak Torque production decreased significantly (*) after Placebo administration (left), but did not significantly change after Riluzole administration (right). B) Maximum voluntary PF Mean Peak Torque did not significantly change after Placebo or Riluzole administration.

Figure 7: Examples of Torque and EMG responses during DF and PF MVCs from two different subjects. In A and B, the top traces show Riluzole administration Pre-Test (black line) and Post-Test (gray line) Torque production (y-axis, in Nm). Time (in s) is shown on x-axis. Bottom traces show Torque and the corresponding EMG responses (in V) for TA, MG, and SOL muscles for the Riluzole Pre-Test (left, in black) and Riluzole Post-Test (right, in gray). Vertical dashed lines indicate the start and stop instructions for the MVC. A) DF Torque and EMG responses for example DF MVC from one subject. Reflective of the sample on average, for this example subject, peak torque did not change following riluzole administration, but the average sustained torque increased significantly. TA EMG activity was maintained through the entire contraction command, and MG EMG activity decreased to 1-2 motor units during and following the command. B) PF Torque and EMG responses for example PF MVC from a different subject.
Neither peak PF Torque nor average sustained torque changed after Riluzole administration. MG EMG activity was also similar in the Riluzole Pre-Test and Riluzole Post-Test.

**Figure 8**: The Avg Sustained DF Torque % Change (post-test minus pre-test with respect to pre-test, y-axis) negatively correlated to Pre-Test MVC Peak DF Torque (x-axis, in Nm) after Riluzole administration (open triangles, dashed line) but not after Placebo administration (filled circles, solid black line).

**Figure 9**: The relationship between the Flexion Withdrawal DF Torque Avg % Difference (with respect to pre-test, y-axis) after drug administration compared to the initial MVC Peak DF Torque (x-axis, in Nm) before (pre-test) drug administration. **A)** After placebo administration, no significant correlation was seen between initial strength and percent change in reflex response at stimulus current intensities 3X Threshold (black triangles, solid line), 4X Threshold (black squares, dashed line), or 5X Threshold (black circles, dotted line.) **B)** After riluzole administration, however, significant correlations between initial strength and percent change in reflex response were seen at stimulus current intensities 3X Threshold (gray triangles, solid line), 4X Threshold (gray squares, dashed line), and 5X Threshold (gray circles, dotted line).
Table 1. Subject sample demographics

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Data was collected from seven subjects with demographics and clinical evaluation scores as shown. Abbreviations: M: male; F: female; T: thoracic; C: cervical; AIS: American Spinal Injury Association (ASIA) Impairment Scale classification (Marino et al. 2003); MAS: Modified Ashworth Score, shown as knee extensors/knee flexors and using a scale of 0-4 with 0 as no impairment and 4 as severe spasticity; SCATS: Spinal Cord Assessment Tool for Spasticity (Benz et al. 2005) shown as extension/flexion/clonus using a scale of 0-3 with 0 as no impairment and 3 as severe spasms lasting longer than 10 seconds; WISCI: Walking Index for Spinal Cord Injury (Ditunno et al. 2000); LEMS: lower extremity motor scores; n/a: not available or unknown. *Subjects A and B were not community ambulatory, while subjects C-G were community ambulatory. Note: MAS and SCATS scores shown are the average score of the pre-test evaluations from both experiment days.
Ankle Torque, Nm

Placebo

Riluzole

Stimulus applied

1 s
Avg Sustained DF Torque vs Pre-Test MVC Peak DF Torque, Nm

% Change

Placebo
Riluzole