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Divergent modulation of clinical measures of volitional and reflexive motor behaviors following serotonergic medications in human incomplete spinal cord injury

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Abstract

An incomplete spinal cord injury (SCI) results in profound impairments in volitional strength and reflex excitability, which contribute to loss of function. Human and animal models suggest that disruption of monoaminergic input, particularly serotonin (5HT), from supraspinal centers contributes this impaired motor function following SCI. In the present study, we investigated the effects of 5HT medications on motor function in individuals with chronic (> 1 yr) SCI. Clinical measures of strength, spasticity/spasms, and walking ability were assessed on 12 individuals with chronic incomplete SCI following acute administration of either 8 mg cyproheptadine, a 5HT antagonist, or 10 mg escitalopram, a selective 5HT reuptake inhibitor (SSRI), in a double-blinded, randomized, crossover fashion. Results indicate that 5HT medications modulate both volitional and reflexive behaviors with little change in walking performance; 5HT antagonist medications depressed clinical measures of strength and spasticity/spasms whereas SSRIs augmented both strength and spasticity/spasms. These changes are consistent with the dysregulation of 5HT-sensitive spinal neurons following SCI. This understanding may augment clinicians' awareness of the motor consequences of 5HT medications.

Key Words: Spinal cord injury, Strength, Spasticity, Spasm, Serotonin

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Introduction

Incomplete spinal cord injury (SCI) can result in profound impairments in motor control and limitations in function. Two prominent, functionally relevant impairments include weakness, defined as deficits in force generation during maximal voluntary effort contractions, and hyperactive reflexes which encompasses spasticity, defined as velocity dependent increases in stretch reflex excitability, and spasms, defined here as sustained, involuntary muscle activation. A variety of pharmacological, physical and/or surgical interventions have been directed towards improving function thorough amelioration of these impairments, although their relative efficacy is unclear.

The mechanisms underlying spasticity and spasms following SCI are multifaceted and include changes in both afferent pathways and spinal circuits. One mechanism underlying spastic motor behaviors that has gained considerable support is the role of altered spinal motoneuron excitability following SCI. Under healthy conditions, synaptic depolarization of the motoneuron is influenced by persistent inward (Ca^{2+} and Na^+) currents (PICs), which amplify and sustain membrane depolarization. Motoneuron PIC activation, and the resulting motor output, is strongly influenced by spinal concentrations of endogenous neuromodulators, in particular serotonin (5HT).[1] The SCI disease progression results in structural changes to these 5HT receptors in the chronic stages post-injury, allowing for PIC activation with minimal residual descending 5HT.[2-4] Dysregulation of PIC activation contributes to the presence of both spasticity and spasms; accordingly, medications which block 5HT activity may decrease spasticity/spasms,[3] whereas medications which augment 5HT bioavailability may increase spasticity/spasms.[5]

Volitional motor output may also be dependent on motoneuron PIC activity. Under healthy conditions, volitional motor tasks produce variable PIC amplification through the activity-dependent release of 5HT.[6, 7] Following incomplete SCI, the loss of descending corticospinal pathways contribute to decreased force generating capacity, while residual 5HT inputs from brainstem centers

may still modulate motor output. For example, PIC activation may help explain the observations of increased time to task failure during sustained motor activity and increases in peak volitional torque generation during maximal effort contractions in patients with incomplete SCI.[8-10] Further, medications which decrease 5HT may decrease volitional strength and functional performance following SCI,[11, 3] where as preliminary data suggests medications which augment 5HT may increase strength.[12, 13]

The current study assesses acute alterations in clinical measures of volitional strength, spasticity/spasms, and locomotor function following single dose administration of 5HT medications in subjects with incomplete SCI. The primary hypotheses were that administration of a 5HT antagonist (cyproheptadine) would depress volitional and reflexive motor function, whereas an agent that augmented 5HT bioavailability, such as a selective 5HT reuptake inhibitor (SSRI; escitalopram), would increase volitional and reflex function. Understanding how these medications affect motor output following SCI may have an important role in clinical decision making, particularly as a large number of individuals with SCI utilize medications which modulate synaptic 5HT activity.

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Materials and Methods

Twelve individuals with chronic motor incomplete SCI participated in a double-blinded, randomized crossover design study to assess the acute effects of over-encapsulated, oral administration of a 5HT antagonist (8mg cyproheptadine, Periactin, Merck Inc.) and a SSRI (10 mg escitalopram oxalate, Lexapro, Forest Pharmaceuticals Inc.) on clinical assessments of motor activity. The dosage of medications was chosen upon previous published and unpublished data.[3, 13] Both medications cross the blood brain barrier and act upon 5HT, among other, synapses in the central nervous system; cyproheptadine acts upon the post-synaptic neuron and blocks ligand-mediated and constitutive activity of the 5HT receptor; escitalopram acts upon presynaptic 5HT reuptake mechanisms to increase the duration/concentration of endogenous 5HT in the synaptic cleft. All subjects underwent a 14 day washout period for anti-depressant, anti-spastic, and all other medications with known interactions with the study agents. All procedures were approved by the Northwestern University Institutional Review Board and all subjects provided informed written consent.

Clinical examinations of strength, reflexes, and locomotor function were conducted prior to and 4.5 hours following administration of either agent, corresponding to peak plasma concentration of study medication. Testing took approximately 30 min and the order of strength, reflexes, and locomotor testing was consistent during each session. A minimum of 7 days separated the 2 testing conditions. The clinical examinations have been described in detail previously with abbreviated descriptions provided below.[12] The Lower Extremity Motor Score (LEMS) is a standard clinical evaluation of strength of 5 lower extremity myotomes (L2–S1; hip flexion, knee extension, ankle dorsiflexion, great toe extension, ankle plantarflexion) bilaterally. Strength is scored on a 0–5 scale, ranging from 'no muscle contraction' to 'normal amount of resistance to examiners efforts' and summed bilaterally for a total possible score of 50. Strength data was also separated by stronger versus weaker limb, and by stronger (≥ 3) versus weaker (< 3) muscle groups.

Lower extremity reflex behaviors were assessed using both the modified Ashworth assessment (mAsh) and the Spinal Cord Assessment Tools for Spastic Reflexes (SCATS). The mAsh assesses resistance to rapid joint movement applied by the experimenter to the passive subject. This evaluation is used to assess spasticity of bilateral knee extensors and flexors using a 0-5 scale ranging from 'no increase in muscle tone' to 'complete rigidity.' Scores were summed bilaterally for a total possible score of 20, with individual assessments also analyzed separately. The SCATS is a clinical evaluation of 3 types of lower extremity spasms (flexor spasms, extensor spasms, plantarflexor clonus). Each spasm is graded on a 0-3 scale based upon the amplitude or duration of reflex activity. Data were summed bilaterally for a total score of 18, with individual assessments also analyzed separately.

Walking function was assessed using an instrumented walking platform (GaitMatII ®, Equitest, Chalfont, PA). Walking data was collected during walking over 2-3 trials at the patients fastest-possible velocity with assistive devices and lower extremity bracing below the knee as needed. Primary outcomes included velocity, step length, and cadence.

Potential differences in clinical measures from baseline values for either medication were assessed using a Wilcoxon Signed Rank; when non-significant changes were observed, baseline measures were averaged. Reliability between baseline testing was assessed using a ICC(2,1) model and the variability was described using the median of the absolute difference between testing sessions. A Friedman's test was used to assess changes between baseline, 5HT antagonist and SSRI conditions. A post-hoc Wilcoxon Signed Rank was used to determine specific differences. Within subject change scores for each medication were calculated and analyzed in a similar manner. Potential correlations among variables were assessed using Spearman Rank. Significance was set at $\alpha=0.05$ for all tests and data in the text is presented as median [25th percentile – 75th percentile].

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Results

Twelve individuals (10 male) with history of traumatic motor incomplete SCI participated in this study. Subjects had a median age of 50.5 [42.5 – 60.5] years and median duration of injury of 93 [63 – 235] months. Two subjects had high cervical injuries (C1 – C4), 7 subjects had low cervical injuries (C4 – C8), and three subjects had thoracic injuries (T1 – T10); using the American Spinal Injury Association (ASIA) Impairment Scale (AIS), 5 subjects were classified as AIS C and 7 subjects were AIS D.

No differences were observed in baseline clinical measures of strength, reflexes, or walking function between testing days (all $p > 0.05$). Baseline clinical measures showed moderate to good reliability with ICC scores ranging from 0.73 to 0.86. The median of the absolute difference between baseline testing sessions was 3.5 [1.5 – 7.0], 1.5 [0.5 – 2.0], and 1.0 [0.0 – 2.0] for LEMS, SCATS, and mAsh values. Baseline walking measures showed excellent reliability with ICC scores ranging from 0.97 to 0.99. The median of the absolute difference between baseline testing was negligible for speed and step length (<0.03 m/s and <0.02 m) while cadence was 2.6 [1.2 – 5.5] steps/min.

Modulation of volitional and reflexive motor output

Participants had a median baseline LEMS score of 41 [34.75 – 45.25]; for reflex behaviors, median baseline mAsh scores were 8.25 [2.5 – 9.25] and SCATS scores were 8.5 [5.75 – 10.75] (Fig 1A–C). There was no significant correlation between baseline LEMS and SCATS values (rho=0.00, p=0.99), although the correlation between SCATS and mAsh values approached significance (rho=0.54, p=0.07). A significant *positive* correlation between baseline LEMS and mAsh values was observed, however (rho=0.65, $p < 0.05$).

Median LEMS decreased to 38.5 [32 – 44.5] following 5HT antagonist administration, and increased to 42.5 [37.5 – 47.5] following SSRI administration. No clear trends in LEMS change scores for individual myotomes were observed ($p > 0.05$), nor when unilateral LEMS scores were

grouped by weaker and stronger sides (p>0.05). Categorizing LEMS change scores for individual

myotomes as either weaker (<3) and stronger (≥3) revealed significant differences between study

medications (p<0.01 and p<0.05 respectively).

For reflex measures, mAsh values decreased to 3.5 [0.0 – 8.0] and SCATS values decreased

to 6.5 [4.75 – 8.5] with 5HT antagonist administration. Conversely, mAsh values increased to 9 [3.5

– 10.25] and SCATS scores increased to 13 [8.0 – 16.25] following SSRI administration. Individual

change scores in these values followed a similar trend (Fig 1D–F). Change scores in individual mAsh

assessments demonstrate significant differences between medications for both knee flexor and knee

extensor spasticity (both p<0.05). Change scores for individual SCATS assessments demonstrate

significance for extensor spasms and plantarflexor clonus (both p<0.05), flexor spasms approached

significance (p=0.06).

Changes in strength and spastic motor behaviors described above appeared to co-vary with

the different 5HT medications. Significant correlations between both LEMS and mAsh change

scores (rho=0.53, p=0.01, Fig 2A), and LEMS and SCATS change scores were observed (rho=0.54,

p<0.01, Fig 2B).

Modulation of walking performance

For measures of walking performance, the median baseline walking speed was 0.71 m/s

[0.49 – 0.90], with a median stride length of 0.55 m [0.47 – 0.59] and cadence of 75 steps/min [66 –

93]. Following 5HT antagonists, median gait speed decreased significantly to 0.66 m/s [0.36 – 0.82]

(p<0.05) and were mediated by reduced stride length (0.53 m [0.39 – .60]; p<0.05), but not cadence

(73 steps/min [64 – 91]). In contrast, SSRIs resulted in non-significant decreases in walking speed

(0.63 m/s [0.44 – 0.77]), stride length (0.51 m [0.44 – 0.57]), and cadence (71 steps/min [66 – 87]).

There were no significant correlations between changes in gait speed and changes in clinical

measures of strength or spastic motor behaviors (all p>0.05).

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Discussion

In the present investigation, single-dose administration of medications which modulate 5HT bioavailability demonstrated divergent trends in motor function in subjects with motor incomplete SCI. Namely 5HT-antagonists decreased clinical measures of both strength and spasticity/spasms, while administration of SSRIs augmented both behaviors. Acute administration of either medication appears to be ineffective at improving locomotor function.

Serotonergic modulation of motor output

The finding that volitional strength and spastic motor behaviors co-vary following different SSRI medication is of primary interest in the current study. In addition, significant correlations in baseline clinical measures of strength and spasticity (mAsh), but not spasms (SCATS), were observed. Though difficulties exist in distinguishing voluntary versus involuntary contractions with clinical measures, the combined findings are consistent with the hypothesis that common neural pathways underlie selected voluntary and involuntary behaviors. Potential mechanisms underlying such changes include modulation of passive and active (PIC) properties of spinal moto- and interneurons, in addition to separate modulatory effects on afferent and descending pathways. The coupling of reflex and volitional motor output may also be seen during quantitative assessments, as reflex activity in individuals with SCI can strongly influence static and dynamic volitional behaviors.[10]

Changes in strength and reflex activity were relatively consistent following either medication, with few outliers from different subjects on separate testing days, (see Figure 2). However, a rather large increase in SCATS values was observed following SSRI medication (Figure 1F). This behavior may be related to the time-dependent assessment of extensor and clonic spasms in the SCATS and suggests that increased persistence of spasms with SSRIs may account for the large differences.

Despite this observation, the general correlations between medication-induced changes in strength and spasticity/spasms were observed.

Walking performance decreased following administration of either 5HT medications, although only significantly following 5HT-antagonists. These findings contrast with previous investigations that demonstrate improved walking ability following longer-duration cyproheptidine administration in patients with incomplete SCI.[14, 15] This decline may have been due to recruitment of relatively higher functioning patients in the present study, where one subject presented with a LEMS of 50. However, all patients demonstrated substantial gait impairments at baseline, with little potential for ceiling effects. Mechanisms underlying this immediate decline in speed following either medication are unclear, as both strength and reflex activity contribute to locomotor function. A likely contributing factor was use of altered neuromuscular control strategies following either medication, with limited time allowed for subjects to adapt to the agents. As such, subjects may have chosen to walk at slower, more stable speeds. Long term application of these medications may allow adaptation to the changes in neuromuscular excitability.

Clinical implications

Despite significant, immediate changes in motor impairments following either 5HT agent, an important clinical implication is the lack of substantial positive improvements in functional walking performance. While the use of SSRIs to improve motor function following neurological injury has been suggested,[16] animal and human studies suggest combined pharmacological and physical (training) interventions to maximize therapeutic benefits.[17, 18] However more data is required as recent studies also suggest that use of SSRIs may contribute to poorer rehabilitation outcomes.[19]

While the motor consequences of these agents are of primary interest, the use of SSRIs in SCI is common,[20, 21] and the resultant side-effects may not be well-understood. As such, patients may be prescribed anti-spastic agents to counteract the observed increase in spasticity with SSRIs. Use of

multiple medications is common in SCI, and may increase risk of drug interactions in addition to a

host of adverse effects.[22-24] Use of medications to treat side-effects of other medications could be

avoided if SSRI-induced increases in spasticity/spasms were accounted for through coordinated,

interdisciplinary medical management.

Conclusion

Acute administration of 5HT medications modulates both volitional and reflexive behaviors in humans with chronic incomplete SCI. 5HT antagonists will decrease clinical measures of strength and spasticity/spasms where as SSRIs will increase clinical measures of strength and spasticity/spasms. These data suggest 5HT may have actions on pathways common to both voluntary and involuntary force generation. Though further work is targeted at elucidating the precise physiological mechanisms underlying the changes observed, the understanding that serotonergic medications alter motor function following SCI may have immediate clinical implications and can increase the clinicians' awareness of motor consequences of medications that alter the bioavailability of 5HT.

Author Disclosure Statement

No competing financial interests exist.

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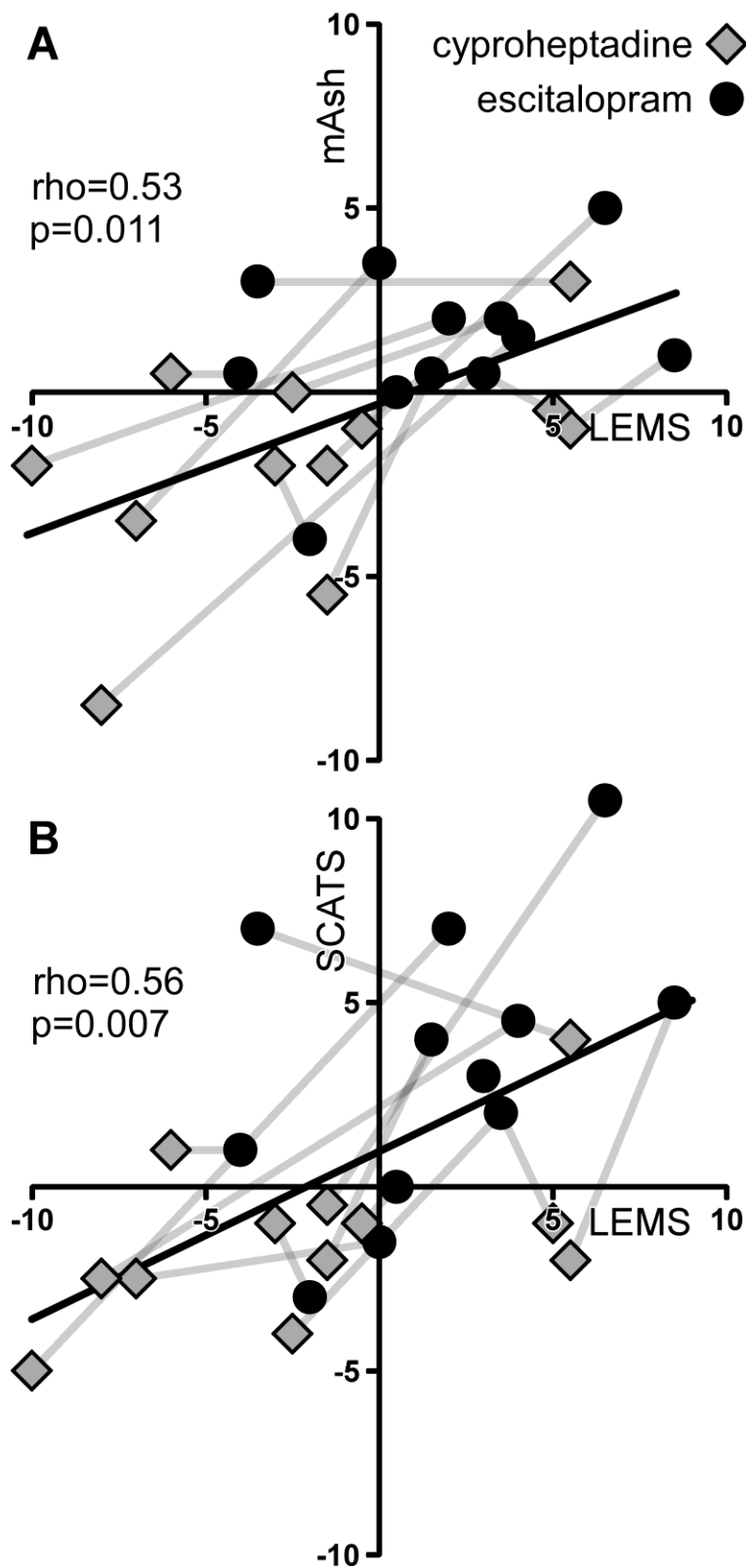
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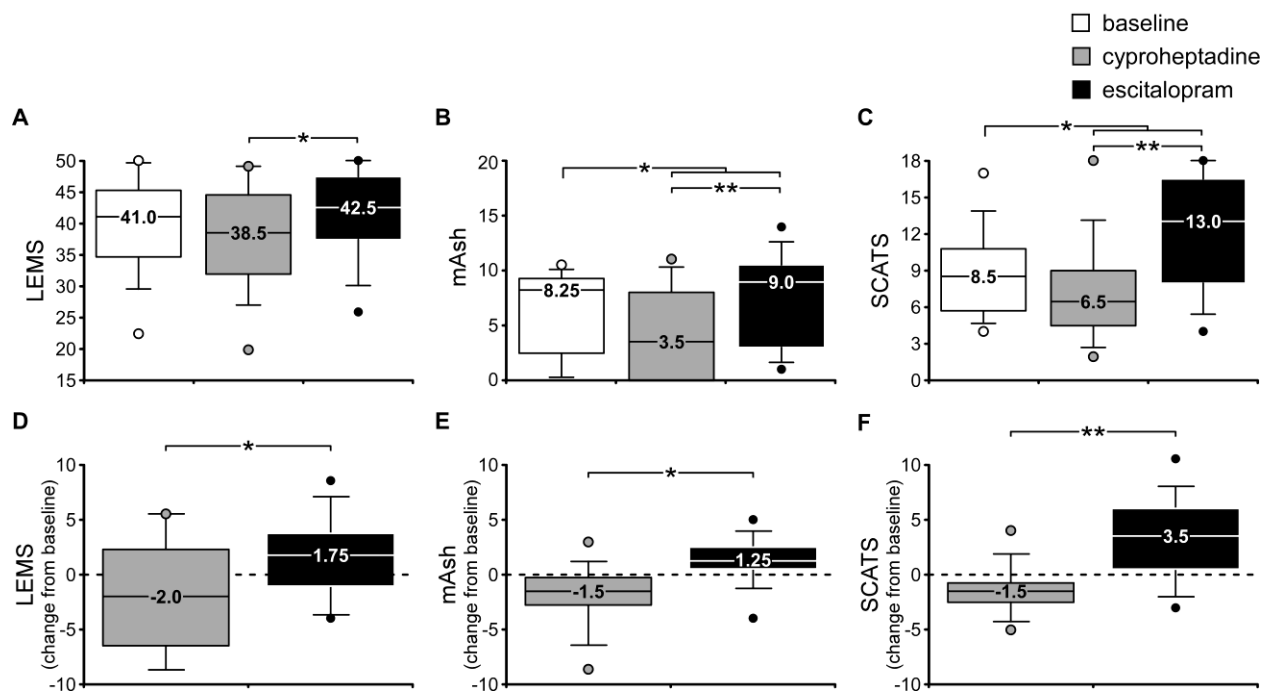
Fig. 1. Assessments of volitional and reflexive motor behaviors following administration of serotonergic medication in patients with motor incomplete SCI. (A–C) Median LEMS, mAsh and SCATS scores are shown during baseline conditions and following either 5HT-agonist (8 mg cyproheptadine) or a SSRI (10 mg escitalopram) (D–F) A median change of 1.25 to 3.5 is observed when individual change scores are assessed. Dashed line indicates no change from baseline and is provided for visual reference. * indicates p< 0.05; ** indicates p<0.01

Figure 2

Fig. 2. Correlation between volitional and reflexive motor behaviors following acute administration of serotonergic medication in patients with motor incomplete SCI. Change in LEMS values are positively correlated with changes in both (A) mAsh and (B) SCATS values.