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Increased Lower Limb Spasticity but Not Strength or Function Following a Single-Dose Serotonin Reuptake Inhibitor in Chronic Stroke

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Abstract

Objective: To investigate the effects of single doses of a selective serotonin reuptake inhibitor (SSRI) on lower limb voluntary and reflex function in individuals with chronic stroke.

Design: Double-blind, randomized, placebo-controlled crossover trial.

Setting: Outpatient research setting.

Participants: Individuals (N=10; 7 men; mean age ± SD, 57±10y) with poststroke hemiplegia of >1 year duration who completed all assessments.

Interventions: Patients were assessed before and 5 hours after single-dose, overencapsulated 10-mg doses of escitalopram (SSRI) or placebo, with 1 week between conditions.

Main Outcome Measures: Primary assessments included maximal ankle and knee isometric strength, and velocity-dependent (30°/s–120°/s) plantarflexor stretch reflexes under passive conditions, and separately during and after 3 superimposed maximal volitional drive to simulate conditions of increased serotonin release. Secondary measures included clinical measures of lower limb coordination and locomotion.

Results: SSRI administration significantly increased stretch reflex torques at higher stretch velocities (eg, 90°/s; *P*=.03), with reflexes at lower velocities enhanced by superimposed voluntary drive (*P*=.02). No significant improvements were seen in volitional peak torques or in clinical measures of lower limb function (lowest *P*=.10).

Conclusions: Increases in spasticity but not strength or lower limb function were observed with single-dose SSRI administration in individuals with chronic stroke. Further studies should evaluate whether repeated dosing of SSRIs, or as combined with specific interventions, is required to elicit significant benefit of these agents on lower limb function poststroke.

Keywords: Muscle spasticity, Muscle strength, Rehabilitation, Serotonin, Stroke

List of abbreviations

- 5-HT, 5-hydroxytryptamine (serotonin);
- MG, medial gastrocnemius;
- MVC, maximum volitional contraction;
- SCI, spinal cord injury;
- 6MWD, 6-minute walking distance;
- SSRI, selective serotonin reuptake inhibitor;
- TA, tibialis anterior;
- UMN, upper motor neuron

Unilateral stroke produces the characteristic upper motor neuron (UMN) syndrome, which includes "positive" signs of spasticity[1,2] and "negative" signs of hemiparesis[3,4] and disrupted coordination.[5,6] While increased spasticity is considered a major barrier for recovery of function,[1,7,8,9] evidence suggests that weakness is the primary determinant of motor function of both lower and upper extremities.[4,10,11,12,13] Most strategies to enhance strength poststroke focus on physical

training and electrical stimulation paradigms, whereas pharmacologic interventions are directed primarily to decrease spasticity[14,15,16] rather than to increase strength.

Previous data suggest that selective serotonin reuptake inhibitors (SSRIs) may mitigate weakness[17] and improve function poststroke.[18,19,20] In general, SSRIs facilitate 5-hydroxytryptamine (serotonin) (5-HT) transmission by decreasing presynaptic sequestration in axon terminals originating primarily from brainstem (raphe) projections.[21] Such pathways are active during wakefulness with increased activity during rhythmic, repetitive movements such as locomotion.[22,23] While the central effects of 5-HT are complex, the net result on motor systems is excitatory.[24,25] In humans poststroke, most studies using SSRIs or other 5-HT reuptake inhibitors (eg, fluoxetine, paroxetine, venlafaxine) focus on the upper extremity and indicate enhanced cortical excitability and motor performance in subacute and chronic stroke (grip strength, rate of finger tap, and 9-hole peg test[17,20,26]). Interestingly, with repeated SSRI administration, data from intact individuals demonstrate potential decreased motor cortical excitability,[27,28] while studies[19,29] with patients early poststroke undergoing rehabilitation indicate improved motor recovery. Although changes in lower extremity function have not been well studied poststroke, single-dose SSRI (escitalopram) administration may improve leg strength in chronic, incomplete spinal cord injury (SCI).[30,31]

Despite the focus on increased supraspinal excitability with SSRIs, these agents may also increase spinal excitability.[32,33] For example, longstanding and recent data in human SCI[30,31,34] suggest increased spastic motor activity after single or repeated doses of SSRIs, although similar findings have not been reported in patients with stroke. In 1 study,[35] greater antagonist muscle activity was observed during volitional upper extremity motor tasks after use of an SSRI poststroke, with no changes in strength or task performance. However, spasticity was not assessed. Whether the findings of increased spasticity with SSRIs are selective to patients with SCI or attributable to differences in the extremities tested is not clear. Increased spasticity with SSRI administration poststroke may be of interest to rehabilitation professionals because spastic hypertonia with

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UMN syndrome is still considered by many to be a major barrier to functional recovery.[8,9]

The objective of this study was to determine the effects of single SSRI doses on lower extremity motor function in patients with chronic stroke. Using a double-blind, randomized, placebo-controlled crossover design, we hypothesized that SSRIs would increase volitional strength in patients with chronic hemiparesis poststroke, consistent with data from upper extremity studies and patients with incomplete SCI. We focused on the single-dose effects here to minimize potential habituation with repeated SSRI use,[27,28] and because of the potential increase in spasticity that may interfere immediately with lower limb function or patient comfort. Considering the potential effects on spinal excitability,[36,37] we also evaluated the effects of SSRIs on stretch reflexes during passive (resting) conditions, and during and after rhythmic, repeated volitional tasks designed to simulate conditions of increased 5-HT release.[22,23] The immediate effects of SSRIs on lower limb motor function are of clinical interest given their common use for treatment of depressive symptoms in this patient population,[38] and the potential consequences of altering motor function during functional tasks.

Methods

Participants

Individuals with chronic (>1y) hemiparesis after unilateral supratentorial stroke, and lower extremity Fugl-Meyer scores <34[39] were recruited. Additional criteria included passive ankle range of motion from 0° to 30° plantarflexion, Modified Ashworth Scale score ≥1 of the paretic plantarflexors,[40] and the ability to ambulate without physical assistance but with assistive devices and below-knee orthoses if necessary. Exclusion criteria included use of oral antispastic medications <14 days previously or receiving a botulinum toxin injection <6 months ago, the presence of uncontrolled cardiorespiratory or metabolic diseases, or having a score <23/30 on the Mini-Mental State Examination.[41] Written consent was obtained from all subjects, with procedures approved by the local ethics committee. A sample size of 10 individuals was targeted from previous

findings in patients with stroke with fewer subjects (n=4–8[17 and 20]) and data of altered volitional strength after single-dose SSRI assessments in human SCI.[30] Power analyses from the latter data indicate that 10 subjects would provide 91% power (effect size, 1.34).

Study protocol

Subjects were randomly assigned to receive 10mg of escitalopram on day 1 and placebo (microcrystalline cellulose) on day 2, or with the order reversed. The half-life of escitalopram is 27 hours,[42] and 7 days between testing ensured drug elimination before reassessment. Agents were overencapsulated and block randomized (4 subjects per block) by the pharmacist who maintained blinding. Subjects were tested before and 4 to 5 hours after drug administration (time for peak plasma concentration[42]). Testing was completed in 1.5 to 2 hours, and the time of day was similar for all procedures across drug conditions (ie, morning for pretesting, afternoon for posttraining). The randomization code was broken after all completed analysis. Figure 1 provides a schematic of the study design.

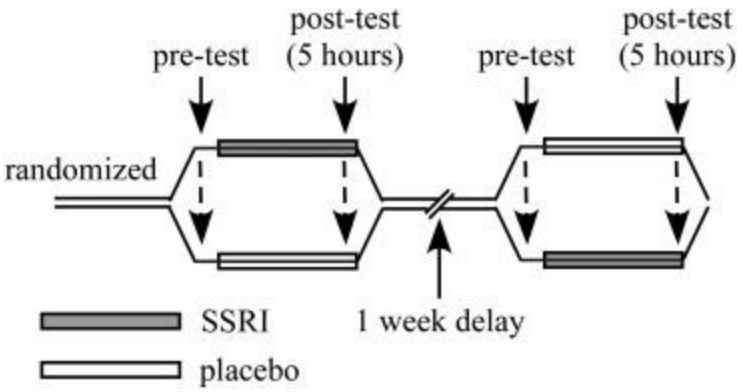

Fig 1. Schematic of study protocol and timing of testing.

Experimental session

Biomechanical measures of lower extremity strength and reflexes, and clinical assessments were performed in the same order during each session. Clinical assessments were obtained in the beginning of each session and consisted of lower extremity Fugl-Meyer scores, 6-minute walking distance (6MWD) at subject's normal comfortable speed, and the fastest gait speeds over 10m.

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Biomechanical measures were obtained using an isokinetic dynamometer (Biodex[a]) with an attached 6-degree-of-freedom load cell.[b] For ankle measures, subjects were seated with the foot secured in a footplate coupled to the load cell/Biodex, and the ankle and Biodex motor axes were aligned,[43] with the knee and hip at 0° and 75° flexion, respectively. For knee measures, the Biodex and knee axes were aligned with the shank secured to an attachment. Position and velocity signals were recorded from Biodex transducers. All signals were sampled at 1000Hz using data acquisition cards and custom software.[c] Surface electromyographic activity was recorded by active electrodes[d] on the paretic tibialis anterior (TA), medial gastrocnemius (MG), and soleus. Signals were amplified (1000×) and filtered (20–450Hz) before sampling. Torque and electromyographic signals were measured during the following tasks: maximal volitional contractions (MVCs) of knee flexion/extension and ankle plantarflexion/dorsiflexion; passive paretic plantarflexor stretches; and passive and active-assist stretch responses. To normalize electromyographic measures, the maximum M wave was elicited through 1-millisecond stimuli applied to the tibial or peroneal nerve to elicit a maximum response of paretic TA and MG recordings.

Isometric MVC tasks

Three MVCs, each 3 to 5 seconds in duration, were performed with ≥60 seconds of rest between trials. MVCs were tested in neutral position (90° angle) for plantarflexion torques and at 30° plantarflexion for dorsiflexion MVCs. Knee extension MVCs were performed at 90° flexion and knee flexion MVCs at 30° flexion.

Passive plantarflexor stretch

Torques and electromyographic activity were measured during passive, paretic plantarflexor stretch through controlled velocity (ramp) ankle rotations from 30° to 0° at constant speeds (5, 30, 60, 90, or 120°/s). Each stretch was held for 10 seconds, and 3 stretch reflexes were recorded at each speed with ≥60 seconds between trials.

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Passive and active-assist trials

Repeated MVCs during controlled ankle movements were performed to assess the effects of SSRIs on combined volitional and reflex behaviors during tasks that presumably increase brainstem 5-HT release.[22,23] These effects were assessed during 6 consecutive cycles of passive and active-assist trials at 60°/s through the 30° range, with 3 seconds between rotations. Subjects relaxed during the first cycle (passive cycle), followed by 3 repeated, concentric MVCs of paretic dorsiflexors and plantarflexors during the second to fourth joint rotations (active assist cycles), and then 2 subsequent passive cycles (fifth and sixth cycles). Subjects were provided verbal cues to start each MVC approximately 1 second before passive movement.

Data analysis

Custom MATLAB[e] programs were used to analyze data. Torque signals were low-pass filtered at 20Hz (fourth-order Butterworth filter applied forward and backward). Torque and angle data during slow (5°/s) stretches were fitted with sixth-order polynomials and subtracted from faster trials to differentiate gravitational/passive torques from reflex response.[44] Electromyographic data were band-stop filtered at 55 to 65Hz. The root mean square electromyographic activity was calculated using a 50-point moving window. The electromyographic signal was normalized to the M-wave amplitude from TA and MG obtained during each session. Recordings from the soleus were nondetectable in 5 of 10 subjects, and only TA and MG data are presented.

During MVC trials, peak torque was calculated as the average torque at a maximum ±25-millisecond window, whereas agonist and antagonist mean root mean square electromyographic activity was determined using a 50-millisecond window at 50 milliseconds before maximum torque. Antagonist muscle co-contraction was quantified by dividing the antagonist muscle electromyographic activity by the agonist electromyographic activity of the same muscle acting as an antagonist (eg, MG co-contraction during plantarflexion was as follows: [MG electromyographic activity during dorsiflexion MVC]/[MG electromyographic activity during plantarflexion MVC]). During passive

trials, stretch reflexes were quantified as the peak plantarflexor torque during movements into dorsiflexion, with MG electromyographic activity quantified at that torque, and averaged at each speed (30–120°/s). For the passive and active-assist trials, analysis focused on plantarflexor activity during dorsiflexion, with plantarflexion torque and mean MG electromyographic activity calculated during the mid-50% ramp of each active-assist cycle. Two passive and active-assist trials were averaged.

Statistical analysis

SPSS version 19[f] was used for statistical analysis with α=.05. No order effects were observed, and all data are compared between drug conditions. For MVC testing, the percent increases (post/pre) in torque and electromyographic activity were also compared between drug conditions using paired *t* tests. Torques and electromyographic responses during the passive and passive-active assist trials were compared using repeated-measures analysis of variance with testing condition (stretch velocity or trial number) and test condition (placebo or SSRI) as main factors, with post hoc Tukey-Kramer or paired comparisons. Pearson correlation coefficients were calculated to evaluate correlations between SSRI-induced changes in torque, clinical measures (Fugl-Myer, gait speed, 6MWD), and demographic characteristics (age, time since stroke).

Results

Eleven subjects were eligible and initiated the study, although 1 felt "light-headed" 1 hour after SSRI ingestion and terminated participation before posttesting, with no adverse effects on follow-up. A total of 10 subjects (7 men) completed the entire experimental protocol. The mean age ± SD of the participants was 57±10 years, and the duration poststroke ± SD was 9.1±7.6 years. Patients presented with either ischemic (n=6; 4 cortical, 2 subcortical) or hemorrhagic (n=4) stroke (see table 1 for demographics). Four individuals received SSRIs during the first test.

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Table 1. Demographics of 10 subjects who completed the study

Subject No.	Sex	Age (y)	Paresis (R/L)	Pathology	Chronicity (y)	FM Score (1st Pretest)
1	M	50	L	Ischemic	5	20
2	M	53	R	Ischemic	4	23
3	F	60	R	Hemorrhagic	4	18
4	M	71	R	Hemorrhagic	19	23
5	M	61	R	Hemorrhagic	11	16
6	F	35	R	Ischemic	8	16
7	M	50	R	Hemorrhagic	3	15
8	M	65	L	Ischemic	6	18
9	F	60	R	Ischemic	5	19
10	M	64	L	Ischemic	26	18

Abbreviations: F, female; FM, Fugl-Meyer; L, left; M, male; R, right.

Effect of SSRIs on isometric MVCs

A trend of increasing torques was observed with all paretic muscles tested, but with substantial variability and no significant differences after SSRI versus placebo conditions. For example, average plantarflexor torque increased by 25%±45% after SSRI administration (fig 2), but was not different after placebo administration (6%±15%; P=.10). Nonsignificant differences in MG activity were also observed (P=.10), with no differences in co-contraction (P=.45). Similar variable changes were observed with dorsiflexion (29%±79% vs 2%±16%, P=.28) and knee flexion torques (32%±56% vs –1%±33%, P=.07), with no differences in paretic extensors (P>.30). Correlation analyses revealed no significant relationships between baseline Fugl-Meyer scores and increases in peak volitional torques after SSRIs (all P>.05).

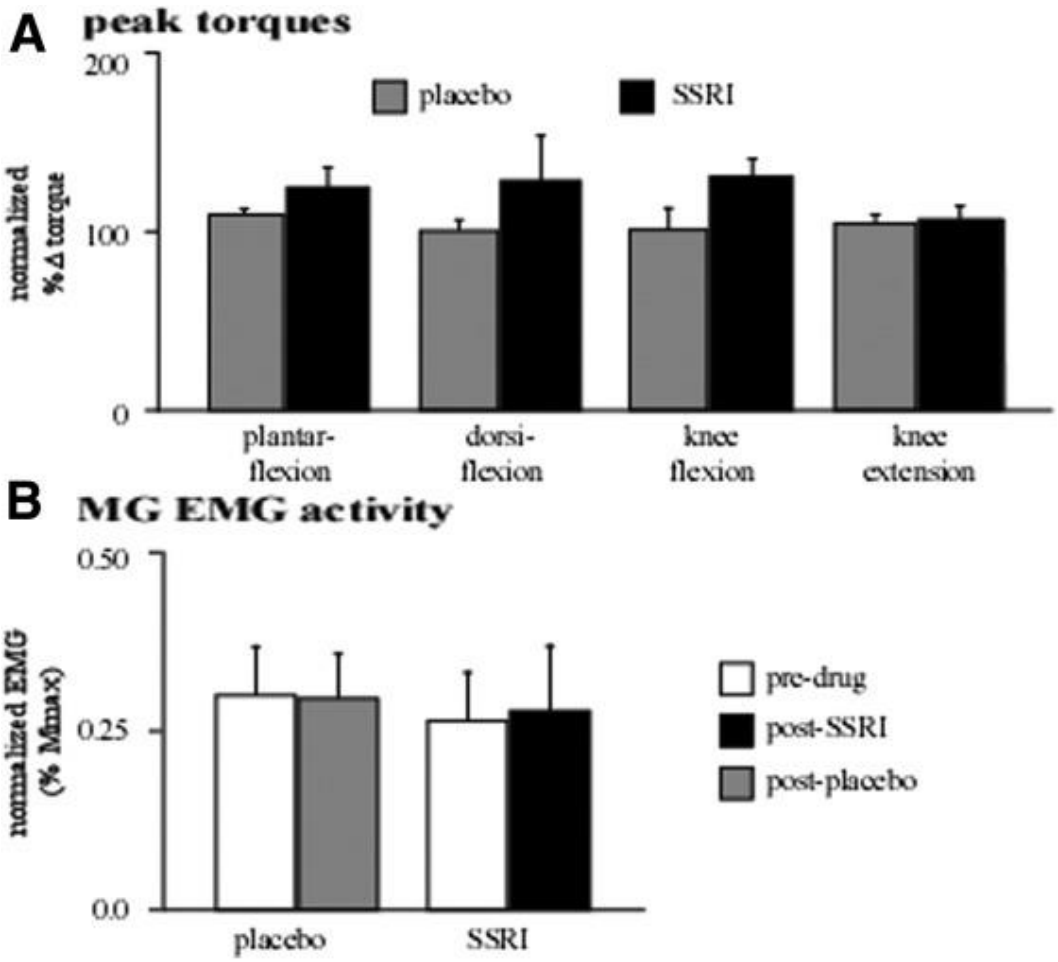

Fig 2. (A) Normalized (pre/post) MVC torques for lower limb muscle groups. Ankle dorsiflexion, ankle plantarflexion, knee flexion, and knee extension torque. (B) Pre- and postplacebo and pre- and post-SSRI MG co-contraction (root mean square MG electromyographic activity during flexion/root mean square MG electromyographic activity during extension) during dorsiflexion MVCs. Error bars represent SEM. Abbreviations: EMG, electromyographic; Mmax, M wave.

Effect of SSRIs on plantarflexor stretch reflexes

Reflex torques generated during passive stretch reflexes varied with stretch velocity, with greater increases post-SSRIs (fig 3A). Reflex torques increased from 30°/s to 120°/s trials in all test conditions (fig 3B). With significant analysis of variance ($P<.05$), post hoc testing indicated reflex torques at 90°/s trials were significantly increased post-SSRI vs placebo (115%±49% vs 48%±47%, $P=.03$). For 120°/s trials, differences in torque approached significance ($P=.08$). Increases in stretch reflex torques post-SSRI were not

correlated with Fugl-Meyer scores or other demographic or clinical data.

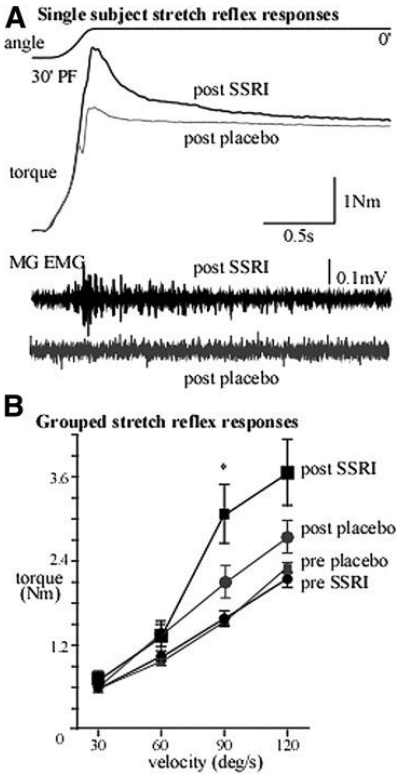

Fig 3. Torque and MG electromyogram (EMG) during stretches of the plantar flexors. (A) Joint angle, torque, and MG EMG are shown for a single representative subject before and after SSRI. The torque in this figure is before subtraction of the passive trials. (B) Grouped mean peak torque generated during the dorsiflexion perturbation ramps (plantarflexor stretch) at different speeds. Error bars show the SEM. **P*<.05. Abbreviation: PF, plantarflexion.

Effect of SSRIs on passive and active-assist responses

The effects of SSRIs on stretch reflexes during superimposed voluntary drive was tested with 6 consecutive stretch cycles, with passive trials for the first, fifth, and sixth cycles, and volitional activity during the second to fourth cycles (active assist). Despite attempts at dorsiflexion during the second to fourth cycles, reflex torques were observed at the end of the movement (fig 4A). As subjects relaxed (fifth to sixth cycles), elevated electromyographic activity and torque measures during rotations reflected the residual effect of volitional drive on stretch reflex excitability, and were compared to the first passive cycle. These effects were enhanced with SSRIs, with

significant repeated-measures intervention for cycle and testing condition. Post hoc comparisons suggested no differences during the first passive cycle (*P*=.87) (fig 4B). During the active-assist cycles (cycles 2–4), plantarflexor reflexes were substantially greater post-SSRI vs placebo (*P*=.08, .02, and .02, respectively). Specifically, increases at the third to fourth cycles were approximately 2.5-fold greater with SSRIs as compared with approximately 1.3-fold greater with placebo. Elevated reflex responses appeared to carry-over into subsequent passive cycles, with torque increases approaching significance at the fifth cycle (*P*=.07) but no differences at the sixth cycle.

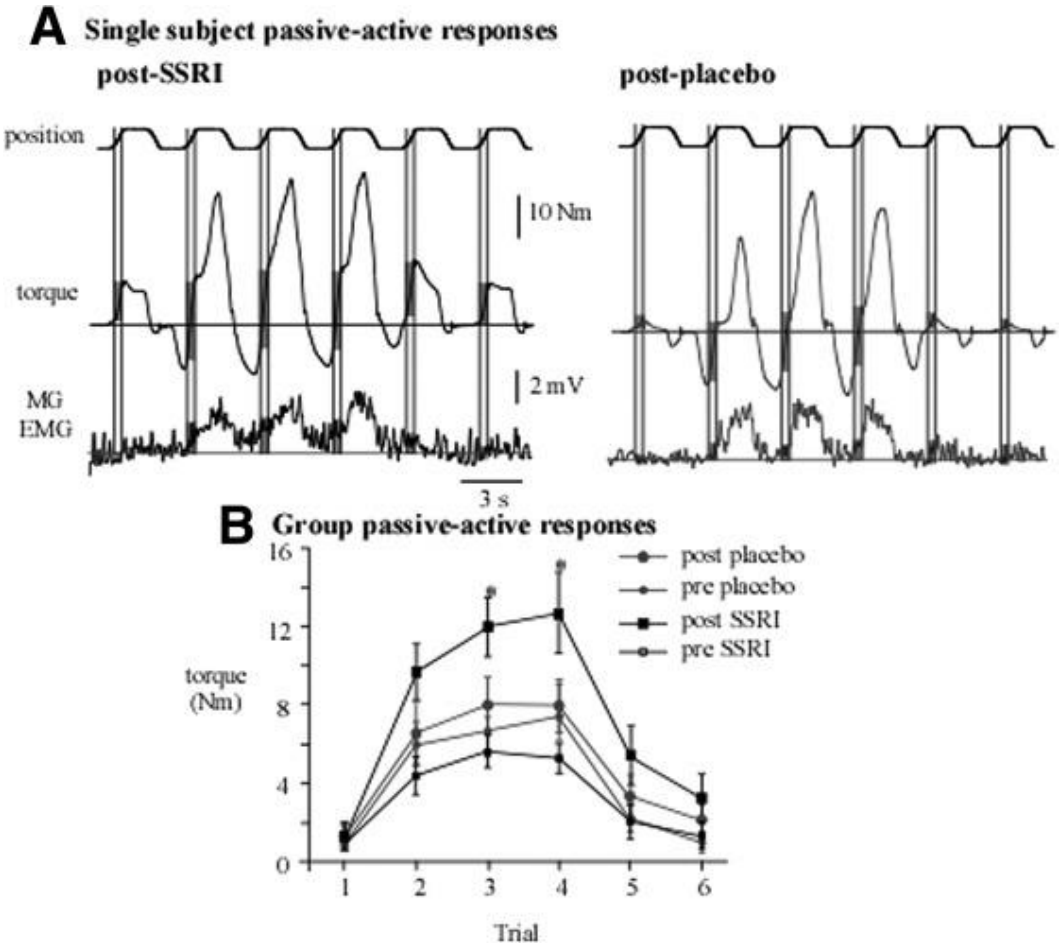

Fig 4. (A) Passive and active-assist trials of a representative subject pre- and post-SSRI. Gray vertical bars represent the middle 50% of the dorsiflexion ramp. The increment in torque and the MG root mean square electromyographic activity that occurred within this interval were calculated. (B) Grouped changes in torques during these intervals across the 6 cycles. Data represent the mean values across 10 subjects with error bars representing SEM. Abbreviation: EMG, electromyogram.

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Clinical measures

There were no differences in changes in 6MWD, fastest gait speed, and lower limb Fugl-Meyer scores across test sessions, with mean changes of less than 10% of baseline after either SSRIs or placebo (fig 5).

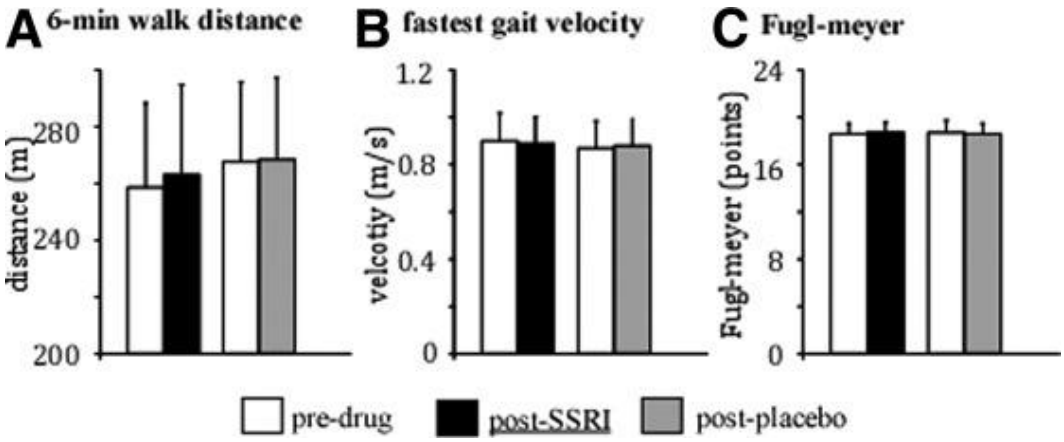

Fig 5. Assessment of motor performance and gait pre- and postplacebo or pre- and post-SSRI. (A) Distance covered during 6-minute walk. (B) Gait speed during fast walking. (C) Lower limb Fugl-Meyer score. Bars represent the average values across all subjects, and error bars show SEM.

Discussion

In the present study, SSRIs demonstrated a significant increase in plantarflexor stretch reflexes in patients poststroke at faster perturbation speeds, which was enhanced with superimposed voluntary drive. No significant increase in any measure of strength or functional outcomes was observed after SSRIs. Increased spasticity has not been reported previously in patients poststroke after SSRI administration, and only studies in patients with SCI have indicated increased SSRI-induced spasticity.

Effects of SSRIs on stretch reflex excitability

Increased stretch reflexes with enhanced 5-HT transmission are consistent with results from animal models with increased descending 5-HT after decerebration, raphe electrical stimulation,[45] or spinalization with 5-HT precursors.[46] We believe increased 5-HT was the likely primary determinant of increased velocity-dependent stretch reflexes

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observed here, consistent with clinical measures of increased spasticity in subjects with SCI.[30,31] Greater increases in stretch reflexes were also observed during the active-assist cycles, with increased activity at speeds (60°/s) at which little effect was seen in the "passive-only" trials. We believe this increased spasticity may be related to elevated descending 5-HT pathways during repetitive rhythmic MVCs,[22] which provided a greater substrate for action of the SSRIs. The resulting 5-HT modulation of spinal circuits[24] could result in depolarization of motoneurons and selected interneurons and amplification of persistent inward currents,[25, 47,48] thereby increasing motor output with specific afferent inputs.

Minimal changes in single MVCs or clinical assessments

The absence of significant gains in MVCs with little co-activation or lack of improvements in functional measures was surprising given the published data in upper extremity studies of patients poststroke.[17,26] One explanation may be assessment of lower extremity function in the present study, where direct cortical projections to lower versus upper extremity motor pools in humans are more limited, such that increased motor cortical excitability may not sufficiently increase descending commands to increase peak force output. However, patients with incomplete SCI demonstrate increases in strength,[30] suggesting that differences in tested populations may also contribute. Conversely, another explanation to account for nonsignificant increases in MVCs is the use of discrete single contractions of a limited duration, which may cause a more limited increase in activity of brainstem 5-HT neurons.[49,50] Single MVCs may not have sufficiently increased 5-HT release, thus providing a more limited response with SSRIs. Indeed, greater changes in upper limb motor function in patients poststroke are observed with brief bouts of task practice, and that may influence the present results.

A related finding was the minimal improvements in walking function. While locomotion is associated with increased 5-HT activity, the nonsignificant increases in strength with significant gains in spasticity could have limited functional performance. More detailed biomechanical and electromyographic analyses during walking after SSRIs are necessary to identify specific locomotor changes,[51]

particularly to indicate whether altered muscle activity contributed to changes in walking function. Regardless, the present data are consistent with selected studies in animal models[52] and humans of neurologic injury (SCI)[51] indicating no immediate improvements in locomotion function with single-dose enhancement of 5-HT transmission. These findings are of clinical interest because previous data suggest improvements in motor function after prolonged SSRI use, although greater changes were observed in upper versus lower limbs.[19] Further study is certainly necessary to address the potential effects of SSRIs on lower limb function poststroke in single or repeated doses and combined with rehabilitation.

Study limitations

The main limitation of the present work is the small sample size. Sample estimates were, however, based on published power analyses on the effects of single-dose SSRI on patients with neurologic injury,[30] although the present sample was sufficient to observe differences in spastic responses. These relative changes suggest "positive" UMN signs may be influenced more in the lower extremity poststroke with SSRIs than weakness. Further studies are necessary to evaluate what clinical or demographic factors determine responsiveness to SSRIs.

An additional limitation is the effects of multiple testing procedures on patient performance and potential fatigue during testing. The use of a randomized blinded trial design with identical order of procedures was necessary to ensure this limitation did not selectively alter outcomes, and this limitation may be difficult to overcome in these and similar studies.

Finally, the present study was limited to the use of only single-dose effects of escitalopram as opposed to other SSRIs that have been tested. The single-dose effects were studied to minimize habituation to the tested agents,[27,29] although greater effects on motor function, including both volitional and reflex behaviors, may be enhanced with prolonged doses.[34] Further, escitalopram was chosen because of potential increased clinical use given its greater efficacy for depressive disorders.[53] Whether similar effects would be observed with other 5-HT agents is not clear, although previous data suggest a similarity in

changes in motor excitability or performance with various SSRIs.[17 and 20]

Conclusions

In summary, single doses of SSRIs did not enhance performance of lower limb voluntary tasks in chronic stroke subjects but rather increased spastic motor activity. This effect was enhanced during repetitive volitional tasks. Increased spastic behaviors with little improvement in function may be considered a potential adverse effect of SSRIs when prescribing these agents to chronic poststroke subjects for depressive symptoms. The lack of improvements in lower limb function with SSRIs may also be important given the results of recent positive trials on upper limb function, and suggests that more work should be done to investigate their global effects.

Suppliers

a. Biodex; Biodex Medical Systems, Inc.
b. Six-degree-of-freedom load cell; ATI Industrial Automation.
c. Custom software and NI-DAQ; National Instruments.
d. Electrodes; Delsys, Inc.
e. MATLAB; MathWorks.
f. SPSS version 19; IBM Corp.

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