ABSTRACT: The consequences of baclofen intake on voluntary motor behaviors remain unclear. We studied the effects of single oral doses of baclofen on voluntary, isometric knee extension torques and surface and single motor unit (MU) electromyographic (EMG) activity from the vastus lateralis in 11 individuals without neurological injury. Examination of sub-maximal to maximal contractions of varying duration performed pre- and post-baclofen ingestion revealed significant decreases in maximal knee torques and EMG magnitude, accompanied by an increase in slope of the torque–EMG relation. A decreased slope of the torque–MU firing rate relation was also demonstrated post-baclofen, but without changes in minimal firing rates or recruitment forces. During sustained contractions at ≤25% of maximal voluntary torque elicited after baclofen ingestion, increased EMG activity was observed without significant differences in MU firing rates. Our results demonstrate a clear reduction in the maximal torque-generating ability following baclofen. Specific changes in MU firing patterns indicate that weakness may be due partly to reduced motoneuronal excitability, although use of MU discharge patterns to assess these effects is limited in its sensitivity.

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CHANGES IN VOLUNTARY TORQUE AND ELECTROMYOGRAPHIC ACTIVITY FOLLOWING ORAL BACLOFEN

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Following damage to descending motor pathways in humans, as occurs in cerebral or spinal cord injury (SCI), individuals often experience weakness and a constellation of involuntary motor signs broadly characterized as spastic hypertonia.38,47 Such signs include spasticity, classically defined as velocity-dependent resistance to imposed passive muscle stretch,28 and spasms or hyperactive multijoint reflexes,35 both of which can present significant barriers to performance of voluntary tasks. The presence of substantial agonist–antagonist cocontraction,49 and dystonia or abnormal posturing,1 can further impair motor performance.

Despite limited understanding of the mechanisms underlying such behaviors, clinical interventions typically consist of administration of various pharmacological agents that target either the central or peripheral neuromuscular apparatus.18 Administration of the gamma-aminobutyric acid (GABA_B) receptor agonist, baclofen, for example, decreases both stretch-evoked spasticity and exaggerated multijoint spasms, and reduces antagonist coactivation during unrestrained or isometric movements (as reviewed elsewhere7). Following oral or intrathecal delivery, some evidence suggests that alleviation of spastic muscle activation after baclofen therapy improves performance of functional tasks, and decreases disability and societal limitations in patients with various neurological disorders.7,11

The mechanisms underlying suppression of spastic muscle activation following baclofen have been studied in both reduced and intact preparations. Traditionally, baclofen has been thought to act primarily at terminals presynaptic to spinal motoneu-
ron (MN) pools. Direct evidence for a definitive presynaptic action for baclofen in humans is lacking, but a postsynaptic action remains a possibility. In reduced preparations, for example, significant depression of MN excitability following baclofen occurs via enhancement of outward K+ currents and suppression of inward Ca2+ conductances. In particular, the long-lasting (L-type) Ca2+ conductance (or persistent inward current) that may contribute to normal patterns of MN discharge is depressed following direct baclofen application in reduced preparations. Suppression of such currents could reduce motor unit (MU) rate modulation in intact vertebrates, including humans, although the effects of baclofen on MU behavior have not been assessed.

The combined results support the view that baclofen induces depression of segmental reflex pathways at multiple sites, which decreases spasticity, but also suggest that baclofen may reduce excitability of neural pathways underlying voluntary tasks. Indeed, one of the major side effects of oral baclofen has been subjective reports of increased weakness and fatigue. Quantitative measurements of changes in voluntary strength following baclofen have, however, produced equivocal results. Specifically, baclofen did not alter voluntary torque production in two separate studies involving subjects with multiple sclerosis. By contrast, in two studies involving individuals with spasticity of varying etiology, baclofen administration decreased maximal torque generation. Such studies have been undertaken only in individuals who have had damage to descending pathways in whom spastic behaviors, in particular antagonist coactivation, can impair performance of voluntary movements. To our knowledge, the effects of baclofen on motor control in individuals without spasticity have not been determined.

Accordingly, the aim of this study was to assess the effects of oral baclofen on maximal isometric voluntary knee extension torques, and on surface and single MU electromyographic (EMG) activity of the vastus lateralis in individuals without neurological injury. Torques and EMG activity were recorded during maximal to submaximal voluntary contractions of variable duration. We hypothesized that baclofen would cause neuromuscular weakness, as evidenced by a reduction in the torque-generating capacity of the knee extensors. Further, we expected that reduction of single MU discharge rates, particularly a decreased slope of the torque–MU firing rate relation, and an increased slope of the torque–surface EMG relation would be suggestive of changes of MN excitability. Establishing the mechanism of action of various antispastic agents in neurologically intact individuals will help elucidate their action in individuals with neurological disorders.

METHODS

Subjects. Subjects between the ages of 19 and 34 years were recruited from the faculty and staff of the Rehabilitation Institute of Chicago. Exclusion criteria included history of significant orthopedic or neuromuscular injury that would impair performance of voluntary knee extension; the presence or a history of hepatic or renal dysfunction that would limit baclofen metabolism or clearance; and use of medication that potentially interacts with baclofen.

Written and verbal consent was obtained from each subject, and all procedures were conducted in accord with the Helsinki Declaration of 1975 and approved by the Institutional Review Board of Northwestern University. Eleven healthy subjects (5 men and 6 women; mean weight, 66 kg ± 15 kg fulfilled the inclusion/exclusion criteria and were enrolled.

Experimental Design. Each subject participated in two identical, experimental sessions of approximately 2 h (separated by 1.5–2 h) to assess the voluntary control of isometric knee extensor contractions before and after baclofen ingestion (total experiment duration ~6 h). Subjects were seated in a chair of adjustable height, facing an oscilloscope positioned approximately 1 m away. The oscilloscope provided a display of the knee extension torque during the experiment, and was used for submaximal, target-matching contractions. During maximal voluntary contractions (MVCs), the oscilloscope was hidden from view to prevent visual feedback. Subjects were secured in place with an adjustable seatbelt at the waist and an adjustable strap was placed around the right upper thigh. The right shank was secured to a load cell with 6 degrees of freedom, with the knee and hip angles set between 90° and 95°. Distances between the knee axis and load cell were recorded to provide an estimate of knee joint torque. Each subject was fitted at identical knee angles and knee axis to load cell distance for both pre- and post-baclofen experimental conditions. All force/torque signals were low-pass filtered (200 Hz) and sampled at 500 Hz by the AD board and stored on a personal computer.

Surface EMGs and single MU action potentials were recorded using active bipolar electrodes (Bagnoli 4; Delsys, Inc., Boston, MA). Surface EMG activity was recorded from the vastus lateralis in all subjects. The vastus lateralis was chosen because of its uniarticular anatomical arrangement and large...
cross-sectional area, compared with other knee extensor muscles. Further, despite previous data suggesting that multiple knee extensor synergists are differentially active during submaximal to maximal voluntary contractions, there are no indications that pharmacological agents may alter the activation pattern between knee extensor muscles during isometric contractions of various magnitudes. The focus of this study was therefore limited to the vastus lateralis in all subjects.

To assess the degree of cocontraction, surface EMGs of the medial hamstrings (semimembranosus/semitendinosus) were recorded during maximal contractions in seven subjects. Surface electrodes were applied to lightly abraded, degreased skin over the respective muscle belly. Electrodes were secured in place by adhesive and were not moved from their position throughout the entire experimental protocol. The signals were amplified (10,000×), filtered (20–450 Hz), and sampled at 1000 Hz.

Single MU recordings were obtained from the vastus lateralis using intramuscular bipolar fine-wire electrodes. Single, bifilar insulated wires were threaded through 30-gauge needles and bent at the inserted end. Following sterilization and skin disinfection, up to two needles were inserted percutaneously up to 2.5 cm into the vastus lateralis muscle belly. Needles were subsequently removed, leaving the wires within the muscle belly. At the opposite (non-inserted) end, insulation was removed from the wires, which were separated and attached to custom-made active preamplifiers. The signals were amplified (10,000×), filtered (20–2000 Hz), and sampled at 5000 Hz using the same computer system used for acquiring the torque data.

**Experimental Procedures.** Each subject was asked to perform four different isometric tasks: (1) MVC trials; (2) target-matched contractions of variable magnitude to obtain torque-EMG relationships; (3) gradually increasing (i.e., “staircase”) contractions at low knee extension torques (<35% MVC); and (4) long-duration (60-s) contractions at 10% and 25% of MVC. Task 1 was always performed first, with tasks 2–4 performed subsequently in pseudorandom order. Single MU behavior was analyzed only for tasks 3 and 4, which were repeated following reconfiguration of fine-wire recordings (and hence alteration of MU sampling) by moving the inserted wires.

**MVC Trials.** Subjects were initially asked to perform up to five maximum voluntary knee extension contractions. With verbal encouragement, subjects increased knee extension torque up to MVC over 1–2 s and maintained the contraction for at least 3 s. Rest between contractions was >60 s. The largest three isometric torque recordings were averaged.

**Torque-EMG Trials.** Subjects were asked to perform isometric knee extension contractions of variable magnitude by matching a target demarcated on the oscilloscope. The target forces ranged between 20% and 80% MVC. Each target force was held for approximately 5 s for three separate trials and separated by at least 20 s to reduce history-dependent effects of preactivation. Subjects performed all trials for each target force sequentially, but the order of target-matching contractions was randomized.

**“Staircase” Trials.** Subjects were instructed to slowly increase knee extension torque by 1.5–2.5% MVC increments with visual feedback from the oscilloscope. Each force was sustained for approximately 3 s, and then increased to the next target force. For each subject, the rate of increase in voluntary torque was kept constant for pre- and post-baclofen contractions, and was confirmed by comparing correlation coefficients of force-time plots using repeated-measures analyses of variance (ANOVA; P > 0.30). Trials were performed at least twice to ensure quality of MU recordings. Starting forces varied from 2.5% to 20% MVC, with the range of torques for any individual trial ≤20% MVC. Maximum torques achieved during staircase trials were <35% MVC.

**Long-Duration Trials.** Subjects were asked to perform 10% or 25% MVC for >60 s using visual feedback provided from the oscilloscope. Subjects rested for at least 2 min following completion of long-duration contractions to minimize neuromuscular fatigue. Long-duration contractions were repeated twice to ensure robustness of MU recordings.

Following completion of all initial tests, subjects ingested orally a maximum single dose (40 mg) of baclofen. All subjects were transferred to a wheelchair and asked to limit ambulation to reduce electrode movement. Surface electrodes remained in their original position throughout the experimental procedures. Fine-wire electrodes either remained within the vastus lateralis or were removed following the initial pre-baclofen measurements. (In 6 of 11 subjects, electrodes were removed during the rest period, and new electrodes were inserted at the onset of the post-baclofen measurements to reduce the possibility of decreased MVC by irritation of the subcutaneous tissues.)

Following oral baclofen administration, peak plasma concentrations are maximal within 2–3 h, with antispastic effects in individuals with neurological injury noted at 2.5–4 h. An approximate 2 h delay was therefore utilized to allow for drug absorption and distribution, and a 2-h window used to study...
the immediate effects of baclofen on control of voluntary knee extension torques. Subjects rested comfortably for 1.5–1.75 h to allow for drug absorption. The first indication of baclofen action for all subjects was the subjective sensation of drowsiness or dizziness, both commonly reported side-effects. Subjects were subsequently repositioned in the recording apparatus at knee angles and load cell to knee axis lengths identical to pre-baclofen conditions. Following repositioning, the experimental protocol was repeated as performed previously in the control, pre-baclofen conditions, with the duration from baclofen ingestion to experimental recordings approximately 2–2.5 h.

**Data Analysis.** All torque, surface EMG, and single MU data were analyzed off-line. For MVC and submaximal torque–EMG trials (tasks 1 and 2), torques and root-mean-square (RMS) EMG values were calculated for the first second during which voluntary torque reached a plateau. Data were averaged across all trials at each desired torque level. Regression and correlation analysis were performed on individual torque–EMG relationships for each subject during both pre- and post-baclofen conditions. Power spectra of the surface EMG signals during MVC trials both prior to and following baclofen ingestion were performed to assess the contribution of neuromuscular fatigue to possible changes in force production. Analysis was performed using custom-designed programs written in Matlab 6.1 (Mathworks, Inc., Natick, MA).

To analyze single MU data (tasks 3 and 4), fine-wire recordings were analyzed using a spike-discriminating algorithm (Spike2, v3; Cambridge Electronic Design, Cambridge, UK). Following a first-pass analysis, identifying templates of MU waveforms and instantaneous firing rates were inspected visually to ensure accurate discrimination of all MUs. For staircase trials (task 3), torque and single MU firing rate were averaged over a 1-s epoch when torque had stabilized at the desired target level. Recruitment threshold for MUs was identified as the percentage of mean MVC during control conditions at which repetitive discharge was observed throughout a 2–3-s epoch of maintained torque. Initial firing rates were identified as the mean discharge rate at the recruitment threshold determined earlier.

For rate modulation data, we analyzed only those units with stable firing patterns detected over at least an 8% MVC range from recruitment threshold (range 8–24% MVC). Further, the rate of increasing torque during staircase contractions was kept between 0.5% and 1% MVC per second, and kept identical in pre- to post-baclofen conditions for each individual subject. Due to the rate-limiting behavior for human MUs at higher forces following recruitment, regression analysis was performed on the individual MU torque–firing rate relations for the entire range of force for which the unit was recruited and the initial 5% MVC following recruitment.

For sustained contractions (task 4), MU data were analyzed as described earlier for staircase trials. Throughout the 60-s contractions, MU firing rates, RMS of the surface EMG, and the mean, standard deviation, and range of target-matched motor torques were sampled over consecutive 5-s epochs. All preliminary analysis of MU firing rates was performed using custom-designed Spike2 software.

**Statistical Analysis.** Changes in maximal knee extension torques, maximum RMS EMG, and the slope of the torque–EMG relation following baclofen were assessed by averaging data across subjects and comparing both absolute and relative changes with the initial control values. Surface EMG activity during submaximal and maximal torques were determined when torques had reached a plateau during a 1-s epoch of data collection, thereby obviating changes in EMG activity due to changes in the rate of rise of contractions. Differences between groups were assessed using a paired Student’s t-test, with significance set at P < 0.05.

For MU recordings, possible movement of fine-wire electrodes over the course of the experimental and rest sessions prohibited discrimination of the same MUs before and after baclofen ingestion. Statistical analysis of changes in MU behavior following baclofen was performed using a two-way analysis of variance (ANOVA) with drug (pre- and post-baclofen) and subject used as independent factors, the latter to account for differences in sampling of MUs between subjects. Differences in recruitment threshold, initial firing rates, and rate modulation (slope of the regression of torque–firing rate relationships) were calculated, with significance set at P < 0.05.

For sustained muscle contractions, RMS EMG values recorded throughout the 60 s were normalized to the value recorded during the initial 5 s of the maintained torque. The relative change in RMS EMG was determined in both pre- and post-baclofen conditions for each subject, and compared using repeated-measures ANOVA at each 5-s interval throughout the duration of the contraction. For MU data, firing rates of only those units discharging throughout the 60-s trials were determined at the initial and final 5-s epochs. Significant differences between initial and final firing rates in both control
and post-baclofen conditions were assessed using paired t-tests. The difference in the decline in firing rate during sustained contraction between pre- and post-baclofen conditions was compared using two-way ANOVA as described earlier, with significance set at \( P < 0.05 \).

**RESULTS**

**Effects of Baclofen on Torque–EMG Relations.** Submaximal to maximal isometric knee extensor torques were recorded before and after baclofen ingestion. In all subjects, both knee extension torques and RMS EMG decreased during attempts at maximum voluntary contractions following baclofen ingestion (Table 1), with the changes correlated significantly \( (r^2 = 0.60, P < 0.01) \). A representative example of these changes is shown in Figure 1A, in which the maximum torque and RMS EMG decreased by 18% and 13% from control values, respectively.

Spectral analysis of the EMG of vastus lateralis activity during MVC trials across all patients revealed no statistical differences in median frequency between conditions (control: mean, 47 ± 11 Hz; post-baclofen: 49 ± 10 Hz; \( P > 0.30 \)), indicating that neuromuscular fatigue did not play a role in the changes observed. Further, there were no substantial changes in the RMS EMG activity of antagonistic medial hamstrings during MVC attempts at knee extension.

Torque–EMG relations were examined by instructing subjects to vary their voluntary isometric force within a 20–80% MVC range by matching a target displayed on the oscilloscope. Isometric torques and RMS EMG of the vastus lateralis across a range of torques were compared, as shown in Figure 1B, with torques normalized to the control (pre-baclofen) conditions. Across the subjects, the relation between torque and RMS EMG was linear both before \( (r^2 = 0.96 ± 0.03) \) and after baclofen ingestion \( (r^2 = 0.97 ± 0.04) \), but with an increase in the torque–EMG slope following baclofen administration. Although the change in slope of this relation was modest (increase in slope is 11% in Fig. 1), the effect was consistent across the subject population and was statistically significant (Table 1).

**Baclofen Effects on MU Behavior.** MU discharge was assessed during low-level, progressively increasing (i.e., staircase) knee extension contractions before and after baclofen administration. Thirty-seven units were recorded in the control condition, and 42 following oral baclofen ingestion in 10 subjects. Recruitment threshold and initial firing rate at recruitment were recorded for all MUs, and the degree of rate modulation (i.e., the slope of the torque–firing

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*EMG, electromyography; MU, motor unit; MVC, maximum voluntary contraction; RMS, root mean square.
‡Sustained contractions: Data provided for the percentage change in RMS EMG of the vastus lateralis from the initial to final 5 s of a 60-s sustained isometric contraction, and changes in single MU firing patterns (initial, final, and decline) in pre- and post-baclofen conditions. Changes in EMG were evaluated using a paired t-test, whereas changes in MU firing were compared using a two-way ANOVA as described earlier.
†Staircase contractions: For MU data, mean ± SD of recruitment threshold, initial firing rate upon recruitment, and the slope of the initial torque–firing rate relation (over the first 5% MVC following recruitment) are shown, with significant differences noted in MU rate modulation between the pre- vs. post-baclofen conditions following use of a two-way analysis of variance (ANOVA) using both drug condition and subject as independent factors.
rate relation) was calculated only for units in which reliable discrimination over a ≥8% MVC range was performed \( (n = 30 \text{ control units; 30 units following baclofen in 8 subjects; mean number of units } \pm \text{ SD per subject: } 3.8 \pm 1.3 \text{ pre-baclofen vs. } 3.8 \pm 1.8 \text{ post-baclofen}) \). Representative examples of the firing behaviors of three MUs that were detected throughout a staircase contraction prior to baclofen ingestion are shown in Figure 2.

Differences in discharge behavior during staircase contractions for a single subject before and after baclofen ingestion are displayed in Figure 3 \( \text{(Fig. 3A: 5 MUs, pre-drug; Fig. 3B: 4 MUs, post-drug). Changes in recruitment thresholds (pre-baclofen: 5.3\% \text{ MVC vs. post-baclofen: 5.4\% MVC) and initial firing rates (5.8 pulses/s vs. 6.4 pulses/s) between the two conditions were not substantially different for this subject, and were not significant across the population of MU data collected from all subjects (Table 1).} \)

In contrast, the degree of rate modulation before and after baclofen administration appeared somewhat different. Discharge rate increased immediately following recruitment in pre-baclofen conditions, and this was followed routinely by a significant decrease in the slope of the firing rate–torque relationship at high force levels (described as rate-limiting behavior\(^4\)). As shown in Figure 3A, all MUs recorded in the control condition demonstrated this initial rapid increase in firing rate. In contrast, only one unit recorded post-baclofen manifested this initial acceleration in discharge upon recruitment.
To characterize the initial acceleration in MU firing rate, the slopes of torque–firing rate relationships were calculated both across the entire range of force (%MVC) of data collection and during the initial 5% MVC following recruitment. For example, in Figure 3A, the comparison for mean firing rate/torque slopes across the full range of discharge was 22 vs. 25 pulses/s/%MVC in pre- vs. post-baclofen conditions, respectively. Conversely, the mean slope of the torque–firing rate relation over the first 5% MVC following initial recruitment was 73 pulses/s/%MVC (pre) vs. 54 pulses/s/%MVC (post).

Averaged data for this subject are shown in Figure 3B, with recruitment threshold and firing rate normalized between conditions to demonstrate the differences in the firing rate/torque slopes. Differences in rate modulation immediately following recruitment were statistically significant between pre- and post-baclofen conditions ($F = 4.496, P = 0.04$; Table 1).

**Baclofen Effects on Long-Duration Contractions.** Single MU and surface EMG activity during sustained (60-s) contractions at 10% and 25% MVC were also investigated. Knee extension torques were maintained within 2% MVC of the desired range during all trials, with no changes in the variability of torque generation ($P > 0.30$). Only MUs displaying repetitive discharge prior to or within the first 5 s of the maintained contraction were analyzed quantitatively [31 pre-baclofen (mean 3.4 ± 1.1 units/subject) vs. 32 post-baclofen (mean 3.5 ± 1.5 units/subject) units at 10% for 9 subjects; 12 units in both pre- (2.0 ± 1.5) and post-baclofen (2.0 ± 1.4) at 25% MVC for 6 subjects]. An example of MU and surface EMG behavior at 10% MVC for both pre- and post-baclofen is shown in Figure 4.

During long-duration contraction trials, two observations emerged. First, although RMS EMG values were not different during the first 5 s in both pre- and post-baclofen conditions ($P = 0.22$), the rate of increase of RMS EMG throughout the contractions was significantly greater following baclofen. During 10% MVC efforts, RMS EMG activity increased 22% from the first to last 5-s epoch in control conditions,
whereas a 40% increase was observed following baclofen ($P < 0.01$; Table 1). Differences in the relative increase in RMS EMG between pre- and post-baclofen trials were significant at 30 s and $>45$ s from the beginning of the contraction (Fig. 5A). The changes in surface EMG activity were accompanied by a significant decline in MU firing rate from the initial to final 5-s epochs for both control ($P < 0.01$) and post-baclofen ($P < 0.01$) conditions. There were, however, no differences in either the initial or final MU firing rates between conditions, and a small, but insignificant difference in firing rate reduction between the two conditions ($F = 3.08, P = 0.09$).

During sustained 25% MVC contractions, we observed significantly different increases in EMG activity for control and baclofen conditions (17% vs. 27%, $P < 0.01$), with statistical significance noted only during the last 10 s (Fig. 5b). Similarly, there were no differences in initial, final, or decline in MU firing rates ($P > 0.30$).

Consistent with increases in EMG activity during sustained contractions, we observed “spontaneous” MU recruitment, in which MUs would begin firing at least 10 s following maintenance of the desired torque, without evidence of substantial changes in torque recordings. An example is demonstrated in Figure 4, in which one MU recorded following baclofen ingestion (D2) began to discharge at $>20$ s following initiation of the contraction.

To quantify these observations, the frequency of onset of MU recruitment following a $>10$-s plateau of desired torque was determined for the initial 10% MVC contractions in pre- and post-baclofen conditions. Examination of all recorded potentials prior to discharge onset of “newly recruited” units was performed to ensure that the units were not recruited earlier and had changed amplitude or shape.

Across all 11 subjects (19 trials with separate MU recordings in each group), 8 MUs were recruited during maintenance of the desired torque during control conditions, and 20 units following baclofen ingestion. A chi-square analysis revealed a statistically significant difference in the frequency of appearance of newly recruited units following baclofen ingestion (chi-square $= 5.14, P < 0.05$). With the decline in firing rate of previously discharging units, recruitment of new units accounted in part for the increased RMS EMG during long-duration contractions.

**DISCUSSION**

Our primary finding was the reduction of maximum knee extension torques in subjects after baclofen administration, which is inconsistent with published reports. Increases in maximal joint torques were accompanied by reduced maximal EMG activity of the vastus lateralis, with no observable changes in medial hamstring EMG activity. During submaximal to maximal contractions, a modest increase in slope of the torque–EMG relation following baclofen ingestion was also detected. Analysis of single MU behavior during low-level, graded contractions re-
revealed a depression of the initial slope of the torque–firing rate relation following baclofen ingestion, but without changes in recruitment thresholds and initial firing rates. During sustained contractions, increases in vastus lateralis EMG were observed in the post-baclofen condition, consistent with a greater onset of newly recruited MUs during these contractions. There were, however, no significant differences in the decline of MU firing rates between the two conditions during the sustained contractions.

**Manifestation of Weakness Following Baclofen.** Previous attempts to demonstrate changes in maximum voluntary torques in individuals with neurological injury following baclofen administration provided equivocal results, with subjective reports of weakness unsubstantiated by independent clinical or quantitative measurements. Conversely, anecdotal case studies have reported decreased volitional drive following baclofen during isometric or unconstrained tasks. It has been suggested that spastic muscles may be useful during functional tasks (e.g., stance phase of gait), and the depression of spasticity may limit functional abilities and could be interpreted subjectively as weakness.

Another potential explanation to account for the discrepancy between subjective and quantitative reports of weakness following baclofen may be its effects on antagonist coactivation. During both isometric and unconstrained movement, individuals with cerebral palsy, stroke, and spinal cord injury demonstrate substantial coactivation of antagonist muscles. Such activity has been shown to decrease following baclofen administration. Diminished cocontraction may offset the depressive effects of baclofen on agonist force generation such that assessment of isometric torques may not change, or possibly increase, with objective measurements. Reduction of antagonist muscle activity is a significant change in impairment, however, and is likely considered during prescription of antispasticity medications to achieve various functional tasks. Nonetheless, such effects may mask the depression of baclofen on generation of muscle force.

In this study, there was no evidence of abnormal antagonist coactivation during isometric contractions in neurologically intact subjects, as was expected. Although the extent of medial hamstring activation during knee extension was not specifically compared with maximal activity during knee flexion, the relative magnitude of medial hamstring activity was unchanged. In subjects without neurological disorders, some coactivation of antagonistic muscles is common during voluntary knee extension contractions, but was not considered a limiting factor for joint torque production. Without substantial alteration in antagonist cocontraction, the effects of baclofen on volitional knee extension torques could be identified, revealing a general decrease across all subjects tested.

**Potential Mechanisms of Baclofen Action.** Attempts to ascribe the changes in motor behavior following baclofen to specific neural mechanisms are necessarily indirect, but involve up to three potential sites: inputs presynaptic to the MN pool; the MN pool itself; and the peripheral neuromuscular apparatus.

To discount the last possibility, the peripheral effects of baclofen are traditionally thought to have been negligible, although a peripheral mechanism of long-term baclofen use has been proposed.

![FIGURE 5. Averaged relative increases in RMS EMG activity (error bars: SE) across all subjects during sustained 10% (A) and 25% (B) MVC contractions (filled squares: pre-baclofen values; open triangles: post-baclofen values). EMG data were analyzed during 5-s epochs over the entire 60 s, and normalized to the value during the initial 5 s of the maintained contraction. Greater relative increases (*\(P < 0.05\); †\(P < 0.01\)) in EMG activity post-baclofen were observed at 30 s and >45 s during the 10% MVC trials, and >50 s during the 25% MVC trials.](image-url)
There are, however, no documented effects of baclofen on M-wave amplitude,\textsuperscript{42,57} and recent evidence has indicated a role for GABA\textsubscript{A}, rather than GABA\textsubscript{B}, receptors on vertebrate skeletal muscle\textsuperscript{6} (c.f., autonomic muscle\textsuperscript{41}). In the recent report by Nielsen and Sinkjaer,\textsuperscript{42} the reduction of twitch torque following supramaximal stimulation after long-term baclofen use may be an indicator of the decrease in net (i.e., spastic and voluntary) muscle activity during baclofen use, which may alter muscle fiber and whole-muscle cross-sectional area. The peripheral effects of baclofen would therefore be indirect, indicating that the mechanisms of baclofen suppression are centrally mediated.\textsuperscript{8,14}

Possible candidates for central nervous system depression presynaptic to the MN pool include both presynaptic inhibition of segmental or supraspinal inputs, or postsynaptic depression of spinal or supraspinal interneurons subserving voluntary force generation. Presynaptic inhibition of afferent inputs has been the mechanism primarily proposed to induce suppression of spastic behaviors. GABA\textsubscript{B} receptor activation at presynaptic terminals decreases Ca\textsubscript{2+} entry to reduce neurotransmitter release,\textsuperscript{9,32,44,45} particularly from afferent inputs.\textsuperscript{10,25} In humans, however, evidence of presynaptic inhibition following baclofen administration is not conclusive. Previous reports have indicated no change in H-reflexes following presumed presynaptic facilitation by femoral nerve stimulation or following vibratory inhibition.\textsuperscript{3} Ørsnes et al.\textsuperscript{43} recently confirmed those findings and also found no change in H-reflexes during disynaptic inhibition following common peroneal stimulation and postactivation depression with slow plantarflexor stretch. The evidence therefore suggests a postsynaptic action of baclofen.

Inhibition of descending inputs presynaptic to MNs may also contribute to weakness following baclofen administration but has not been studied adequately. As stated previously, a common side effect of oral baclofen includes drowsiness, which may reduce supraspinal drive to MN pools. In one study, single (50-mg) doses of baclofen reduced intracortical interneuronal, but not pyramidal, cell excitability in neurologically intact subjects, which, in turn, may reduce descending voluntary drive.\textsuperscript{57} The paucity of research on the effects of baclofen on descending and spinal interneuronal excitability suggests that further investigation is required.

By extension of the aforementioned findings, an alternative baclofen action may be to promote postsynaptic MN depression. Baclofen has been shown to depress sub- and suprathreshold MN excitability through enhancement of outward K\textsuperscript{+} conductances\textsuperscript{56} and suppression of inward, primarily Ca\textsubscript{2+} currents.\textsuperscript{36,54} Recent evidence suggests that long-lasting Ca\textsubscript{2+} conductances\textsuperscript{24,51} may contribute to normal MU behavior in humans.\textsuperscript{16,17,27} Suppression of these currents by baclofen\textsuperscript{54} could reduce the slope of the torque–firing rate relation if synaptic drive is increased proportionally with increasing torque.\textsuperscript{23} However, direct confirmation of MN depression following baclofen in humans is limited.\textsuperscript{12,45}

The current findings of small, yet significant, changes in selected MU discharge behaviors limits our ability to ascribe the mechanisms of baclofen action to any specific neural locus. We initially hypothesized that depression of rate modulation with concomitant increases in the torque–EMG slopes would be consistent with MN depression. Greater torque EMG slopes have been observed previously in subjects with multiple sclerosis following baclofen intake,\textsuperscript{42} and could be attributed to reduced MN discharge\textsuperscript{3} (see also Capaday,\textsuperscript{8} Fig. 1). Significant changes in torque–EMG slopes and MU rate modulation, which have been observed in the decerebrate cat following dorsal hemisection\textsuperscript{46,50} (i.e., without changes in the peripheral apparatus), support this hypothesis. However, during sustained contractions, we expected a significantly greater decline in MU firing rates post-baclofen, concomitant with changes in surface EMG increases. The greater increase in EMG and recruitment of previously quiescent MUs following baclofen indicate an increased neural drive to maintain joint torque, potentially to offset the reduced firing rates, although differences in firing rate decreases were not statistically significant.

Despite some evidence suggesting MU behavior is altered following baclofen, other structures along the neuraxis may have contributed to the weakness observed, including depression of synaptic inputs. Alteration in synaptic inputs alone cannot, however, account for changes in MU firing unless the effects of baclofen are distributed unequally across inputs to the motor pool. If afferent inputs are indeed selectively inhibited, as suggested previously,\textsuperscript{8,25} their role in amplification of muscle output\textsuperscript{19,34} would be minimized, and increased descending inputs would be required to maintain desired torques. With reduction of afferent input, initial MU firing rates upon recruitment are reduced during voluntary submaximal contractions,\textsuperscript{35} in contrast to the present results. We cannot, however, exclude a reduction in synaptic input as a factor contributing to the changes observed here.

Current techniques to detect pre- vs. postsynaptic mechanisms remain limited. To date, the most thorough studies to investigate the effects of baclofen on spinal reflexes have employed H-reflex changes fol-
lowing specific afferent inputs. In both studies, however, the possibility of MN depression was indirect and suggested by the lack of significant changes in specific presynaptic or interneuronal pathways to MNs. A recently developed technique has suggested that specific inward (Ca^{2+}) currents can be assessed from paired MU firing patterns, although its validity has yet to be established.

**Functional Significance.** The presence of changes in knee extension torques and vastus lateralis surface EMG activity confirms the depressive action of baclofen on volitional motor behaviors, which may be due to postsynaptic MN depression. Despite multiple mechanisms that may be operating to reduce voluntary motor output, the present findings validate previous subjective reports of increased weakness and fatigue in patients with neurological injury. Alternative pharmacological agents that selectively target spastic motor behaviors without causing weakness have been suggested to optimize functional behaviors in subjects with neurological injury. For example, agonists to selective monoaminergic receptors have been suggested to satisfy these criteria, although, in clinical practice, significant side effects limit their usefulness. Further research is therefore required to identify pharmacological agents that maximize voluntary function following suppression of spastic motor activity and also to target the precise neural mechanisms underlying the effects of such agents.

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