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Sensory input to primate spinal cord is presynaptically inhibited during voluntary movement

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During normal voluntary movements, re-afferent sensory input continuously converges on the spinal circuits that are activated by descending motor commands. This time-varying input must either be synergistically combined with the motor commands or be appropriately suppressed to minimize interference. The earliest suppression could be produced by presynaptic inhibition, which effectively reduces synaptic transmission at the initial synapse. Here we report evidence from awake, behaving monkeys that presynaptic inhibition decreases the ability of afferent impulses to affect postsynaptic neurons in a behaviorally dependent manner. Evidence indicates that cutaneous afferent input to spinal cord interneurons is inhibited presynaptically during active wrist movement, and this inhibition is effectively produced by descending commands. Our results further suggest that this presynaptic inhibition has appropriate functional consequences for movement generation and may underlie increases in perceptual thresholds during active movement.

Normal motor behavior stimulates peripheral receptors, generating self-induced recurrent activity. For example, moving our limbs produces time-varying afferent input from cutaneous and proprioceptive receptors that is transmitted to the central nervous system (CNS), where it potentially interacts with motor commands and cognitive processes. The extent to which this re-afferent input is incorporated into ongoing motor and sensory processing remains a key issue in understanding mechanisms of voluntary movement and perception.

Movement-induced feedback arrives via afferent fibers that make synaptic contact with so-called first-order 'relay' neurons in spinal cord that transmit activity to local neural circuits[1] and to higher centers via ascending pathways[2]. These relay neurons represent one of the first stages at which peripheral input could be modulated, so any task-dependent changes in their responsiveness during normal behavior would have significant consequences. To date, the evidence for such changes is largely indirect. For example, ample evidence indicates that muscular and cortical responses evoked by stimulation of peripheral afferents are modulated during voluntary movement. In humans, cortical potentials evoked by stimulation of skin[3] or peripheral afferents[4] are reduced before and during finger movement, and psychophysical thresholds for detecting tactile stimuli are concomitantly increased[5,6]. During human locomotion, reflex muscle responses evoked from cutaneous and muscle afferents are strongly modulated in a phase-dependent manner[7,8]. Because these studies examined overall input-output relations, the site and mechanisms that modulate peripherally evoked sensory and motor responses remain unresolved.

Responses of the relay neurons may be modulated by either presynaptic or postsynaptic mechanisms. Postsynaptic modulation via synaptic inputs would affect the neurons' responses to many inputs, peripheral and descending, whereas presynaptic inhibition could reduce sensory inputs more selectively because it can modify the efficacy of transmitter release from specific afferents[9]. Presynaptic inhibition operates in various relays of the visual[10], olfactory[11] and somatosensory systems[12–15]. It is mainly mediated by axo-axonic GABAergic synapses that produce 'primary afferent depolarization' (PAD) of the afferent fibers[16,17]. PAD reduces the amount of transmitter released by action potentials invading the presynaptic terminals, thus reducing the size of responses evoked in first-order and subsequent relay neurons. In the spinal cord, PAD in peripheral afferent fibers is typically evoked experimentally by a synchronous volley in other afferents or in descending pathways[9].

To date, the degree to which PAD occurs during normal behavior could only be inferred from indirect evidence. Fictive locomotion in immobilized, decerebrate cats is accompanied by phase-dependent modulation of PAD of cutaneous and muscle afferents[18–20]. During active sleep, PAD in muscle afferents[21] and trigeminal primary afferents[22] is enhanced. These studies suggest that PAD could be dynamically modulated, but its operation has not been studied in awake, behaving animals. Sophisticated reflex testing in humans indicates that a decrement of the monosynaptic reflex at the onset of[23] or before[24] movement could involve presynaptic mechanisms, but this evidence is indirect and restricted to muscle afferents. Consequently, the occurrence and role of presynaptic inhibition in normal voluntary behavior remains to be tested directly in intact, behaving animals.

Using new techniques to record the activity of spinal interneurons in awake behaving primates[25] in combination with nerve cuff electrodes to stimulate and record from a peripheral nerve[26], we found the most direct evidence to date that presynaptic inhibition operates in a behaviorally relevant manner during voluntary movement.

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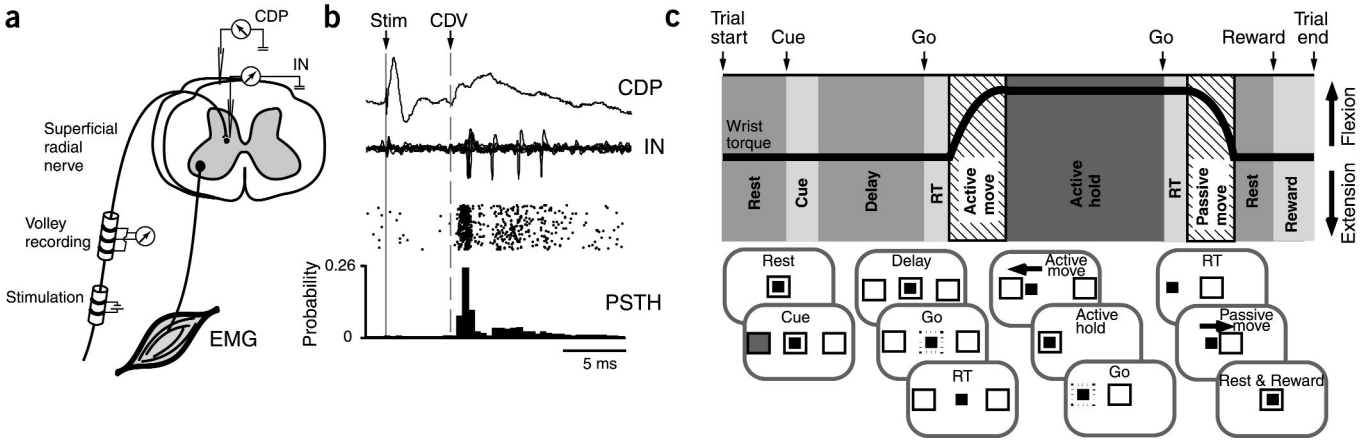

Figure 1 Experimental design. (**a**) Recording setup. Two nerve cuffs were implanted on the SR nerve and microelectrodes recorded cord dorsum potential (CDP) and activity of spinal interneurons (IN). EMG activity was recorded from active forearm muscles. (**b**) Responses evoked by SR stimulation. From top, typical CDP (average of 845 sweeps), responses of spinal IN (7 superimposed traces), raster plot and peristimulus time histogram (PSTH) of IN activity. Segmental latency was measured from peak of cord-dorsum volley (CDV) to the onset of PSTH peak. (**c**) Behavioral task. Typical torque trace during a single flexion trial is shown with task epochs. Diagrams show the cursor controlled by the monkey (small filled square) and targets (larger squares) on video screen. Trials began with the cursor held in a center target window, corresponding to zero torque, for 1.3–1.6 s (rest). Next, the flexion and extension targets were shown to the left and right of the center target. One target was filled transiently (cue, 0.3 s) indicating the correct movement to be performed at the end of the instructed delay period (delay), signaled by disappearance of the center target (go). No wrist movement occurred during the delay period (1.5–2 s) of accepted trials. After a brief reaction time (RT), the monkey moved the cursor to the desired target quickly (active move; less than 1.5 s including RT) and held against an elastic load for a period of 1.5 s (active hold). At the end of the active hold period, the torque target disappeared and the center target reappeared (second go). After a second reaction time (RT), the monkey relaxed the forearm muscles, allowing the servo-spring to passively return the wrist (passive move) to the zero torque position (rest). After keeping the cursor within the center target for 0.8 s, the monkey was rewarded with applesauce for successful trials.

Presynaptic inhibition reduces afferent input to the primate spinal cord during active voluntary movement, with potential effects on movement control and sensory perception. Moreover, the data suggests that this mechanism is evoked more effectively by motor commands than by peripheral input.

RESULTS

To investigate directly the modulation of sensory input during preparation and execution of normal voluntary movements, we recorded the activity of interneurons in the cervical spinal cord of monkeys performing a wrist flexion–extension task with an instructed delay period (**Fig. 1**). Monkeys produced torque against an elastic load that returned the hand to a rest position in the absence of active muscle contraction. Throughout this behavior, interneuron responses were evoked by electrically stimulating the superficial radial nerve (SR), which contains only cutaneous afferents.

Modulation of SR-evoked responses

We report results from 46 first-order interneurons (Monkey K, 38; Monkey M, 8), that responded at monosynaptic segmental latencies (<1.5 ms) after arrival of the cord dorsum volley. Mean segmental latency was 0.97 ± 0.08 ms (mean ± s.e.m.), and the mean activation threshold was 1.79 ± 0.11 times the current needed to evoke a threshold afferent volley. The representative cell in **Figure 2** showed increased activity during active hand movement in both flexion and extension directions (**Fig. 2a**,**c**). In first-order interneurons, much of this movement-related activity could reflect input from peripheral receptors activated during the movement[27,28]. The short-latency responses to SR stimuli are summarized by the post-stimulus histogram peaks compiled for different phases of the task (**Fig. 2b**). These responses were reliably evoked during the pre-trial rest period but virtually disappeared when the monkey actively generated dynamic torque (active movement) and decreased slightly relative to rest during production of static torque (active hold). However, the evoked responses did not decrease significantly during return to the rest position (passive movement). The average firing rates for different phases of the task (**Fig. 2c**) show that interneuron discharge increased during active and passive movements; interneuron activity was larger with the extension movements, which stimulated the receptive fields of SR afferents (the radial side of the dorsum of the hand and distal forearm). In contrast, the responses evoked by SR stimulation decreased significantly only during active movements (**Fig. 2c**). Mean electromyographic (EMG) activity of agonist muscles was highest for the active movement, and muscle activity was absent during the passive movement (**Fig. 2c**).

The averaged results for all 38 first-order interneurons in this monkey (**Fig. 3**) were similar to those in **Figure 2**. Relative to rest, mean firing rates increased most during active movement in both directions, and they also increased to a similar level during passive movement in flexion trials. In contrast, the magnitude of the SR-evoked response decreased drastically during active movements (both flexion and extension) but did not change significantly during passive movements. It should be noted that 34% of the interneurons included in this comprehensive average did not show significant reductions in responsiveness. We found no significant difference in mean firing rate, onset latency or activation threshold between neurons that exhibited the suppression and those that did not. Data from the second monkey (monkey M; $n = 8$) confirmed these findings.

Given that SR-evoked responses in these interneurons were depressed during the period when their firing rates were highest, it is conceivable that the interneurons' background activity could reduce evoked responses through increased refractoriness. To test this possibility, we compared the SR-evoked responses that were preceded by background spikes with those that were not. The responsiveness of

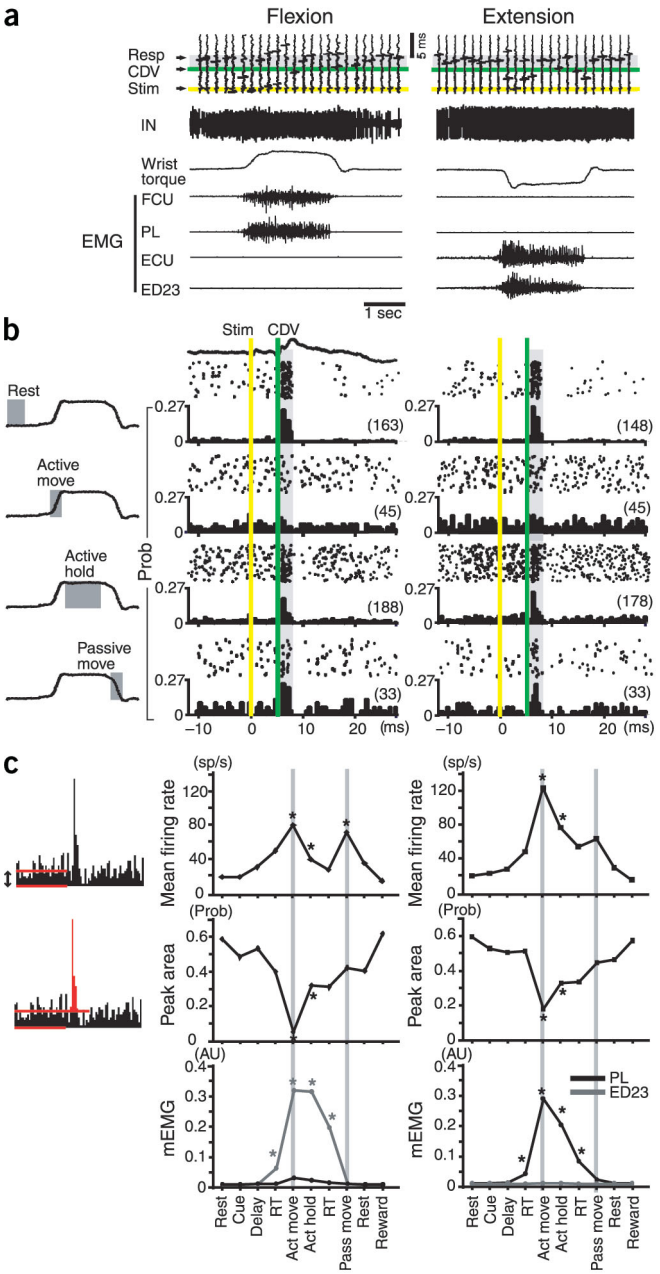

Figure 2 Suppression of SR-evoked response in a first-order interneuron. (**a**) Responses of a C8 interneuron to SR stimulation (top, in fast vertical sweeps) and task-related spiking activity (IN), voluntary torque measured at wrist joint and EMG activity in two flexor and two extensor muscles during flexion (left) and extension (right) trials. Top traces are aligned to the SR stimuli (yellow line). SR was stimulated at 3 Hz at 1.6× threshold for the afferent volley throughout this recording. This interneuron showed responses to stimulation (spikes within the gray shaded box, corresponding to the peak duration period as defined in **b**). FCU, flexor carpi ulnaris; PL, palmaris longus; ECU, extensor carpi ulnaris; ED23, extensor digitorum-2,3. (**b**) PSTHs (bin width, 0.5 ms) below raster plots of the action potentials of the neuron shown in **a**. Each plot was aligned with the SR stimuli (yellow line). Trace above shows the CDP with afferent volley (CDV) marked by vertical green line. Height of each PSTH bin represents the normalized probability of spike occurrence per stimulus. From top to bottom, responses compiled during different task epochs (indicated on torque traces to left): rest, active movement, active hold and passive movement. Number of stimuli delivered in each epoch is given parenthetically with each PSTH. (**c**) Summary of mean firing rate (top) and peak area of evoked response (middle) for each task epoch, calculated as shown by left insets. Mean firing rate was obtained from mean bin height before (50 ms to 1 ms) stimuli. Peak area was sum of bin heights above the mean firing rate during peak. Peak duration was time when the bin counts exceeded two standard deviations of the mean firing rate. Bottom, the mean EMG activity of representative flexor (PL) and extensor (ED-23) muscles. Asterisks indicate significant differences compared to rest, using a Student's *t*-test (top, $P < 0.05$) or a bimodal test (middle, $P < 10^{-2}$; bottom, $P < 10^{-12}$).

the first-order interneurons to SR stimuli did not differ in trials with or without preceding action potentials (**Fig. 3b**), indicating that background firing rate had no significant effect on the reduction of SR-evoked responses during the active movement period. This conclusion is further supported by two additional observations: (i) the rates evoked by more intense SR stimuli exceeded 500 spikes/s, indicating that the cells were capable of firing at rates ten times higher than those evoked during movement (**Fig. 3**) and (ii) the firing rates showed similar increases during active and passive movement in flexion trials without any comparable decrease in the SR response during passive movement (**Figs. 2** and **3**).

Suppression of SR-evoked responses starts before EMG onset

To determine whether the reduction of SR-evoked responses was dependent on feedback from movement, we analyzed the time course of the reduction around the onset of EMG activity. A typical example of a first-order interneuron whose response probability (peak area in peristimulus time histogram, PSTH) dropped 400 ms before EMG activity started ($P < 0.05$) is shown in **Figure 4**. Of the 25 first-order interneurons that showed a suppression of SR-evoked responses during active movement in monkey K, 14 (56%) showed reduction before EMG response onset. On average, the reduction started 400 ms before EMG onset in this population of interneurons (**Fig. 5**, $P < 0.05$). Since there was no muscle activity or wrist torque that could have induced afferent feedback before EMG onset, this early reduction of the monosynaptic response was probably produced by descending commands. Data from the second monkey (monkey M) confirmed these findings (4/8 interneurons showed suppression that started before EMG onset).

Two mechanisms could potentially account for the reduction of the monosynaptic responses to SR stimulation. The evoked responses could conceivably have been reduced by postsynaptic inhibition, but this would be inconsistent with the fact that the interneurons were more active during movements than during rest, reflecting an increase in postsynaptic excitatory drive that would have increased, not decreased, interneuron responsiveness. (It remains conceivable that postsynaptic responses could be reduced at distal dendrites, independently of increased drive at the soma, through 'remote inhibition'—a possibility that has been proposed[29] but not yet proven in spinal interneurons.) A second explanation for the decrease in evoked responses at a time when the cells were more excitable is a reduction of the efficacy of the afferent volleys by presynaptic inhibition[9,17,29].

Primary afferent depolarization during active movement

To further test whether the afferent fibers underwent presynaptic inhibition, we applied Wall's excitability test for PAD[14]. PAD is associated with reduced transmitter release from presynaptic terminals[9,16] and also reduces the threshold of afferent terminals to direct electrical stimulation. This increased excitability of the terminals would produce an increase in the antidromic SR nerve volley evoked by

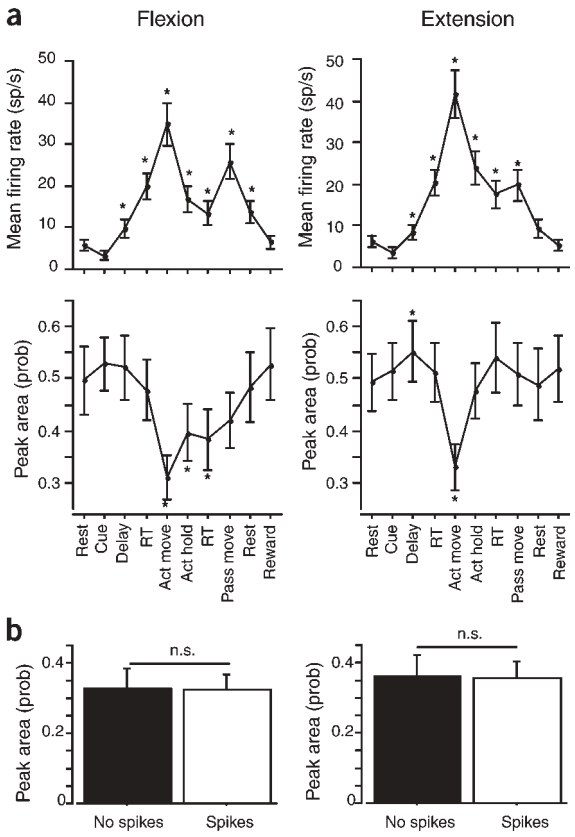

Figure 3 Summary of response modulation and firing rates for all first-order interneurons. (**a**) Averages (± s.e.m.) of mean firing rate (top) and PSTH peak area (bottom) in each epoch obtained from 38 first-order interneurons in Monkey K; left, flexion trials; right, extension trials. *$P < 0.01$ compared to rest, Student's *t*-test. (**b**) Effects of preceding spikes on PSTH peak area during active movement. Bars represent averages (± s.e.m.) of PSTH peak area for 30 interneurons with sufficient background activity, for PSTH compiled from trials with no spikes in the preceding time window (filled) and trials with preceding spikes (open). The time window to measure the existence of preceding spikes was fixed for each neuron and corresponded to its mean interspike interval. Mean firing rate in the 100 ms preceding this time window was 36.7 ± 5.1 Hz (without spikes) vs. 46.4 ± 5.6 Hz (with spikes) in flexion trials, and 44.8 ± 5.5 Hz vs. 53.4 ± 5.7 Hz in extension trials, indicating that differences in this prior activity could not account for changes in the responsiveness to SR stimuli.

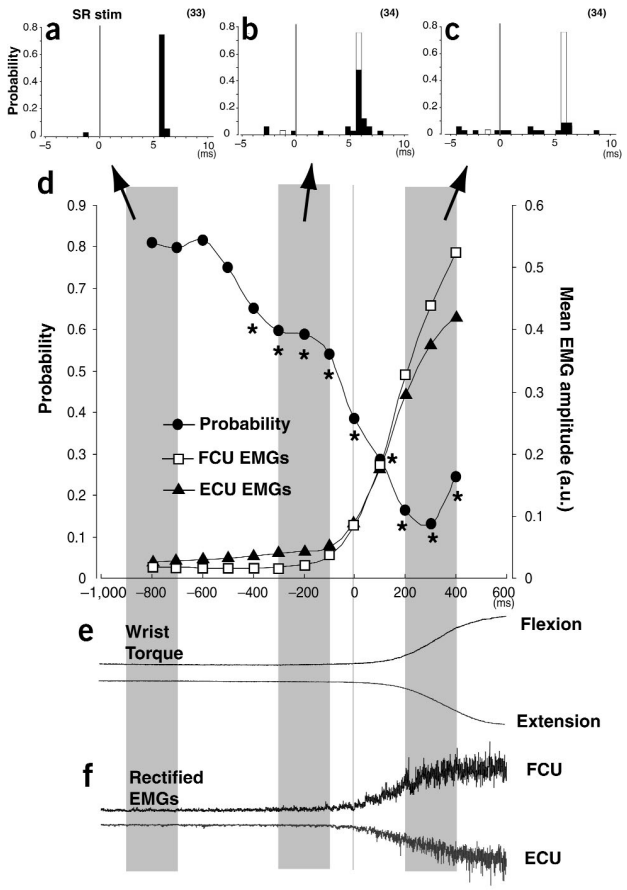

Figure 4 Suppression of SR-evoked response before EMG onset. Mean EMG amplitude and PSTHs of SR-evoked responses were calculated relative to the time that EMG activity began (EMG onset). (**a**–**c**) PSTHs of SR-evoked response during the interval of (**a**) 900 to 700 ms before ($n = 33$), (**b**) 300 to 100 ms before ($n = 34$) and (**c**) 200 to 400 ms after ($n = 34$) EMG onset of flexor (FCU) and extensor (ECU) muscles. For comparison, the histograms in **b** and **c** were plotted over the histogram from **a** (open bars). Note that short-latency peaks were suppressed in **b** and disappeared in **c**. (**d**) Mean EMG amplitude of FCU and ECU, and peak area of the short-latency responses of SR-evoked PSTHs (response probability). Flexion and extension trials were combined in the calculation of peak area. EMGs of FCU and ECU muscles showed the earliest onset of activity among flexor or extensor muscles, respectively. Asterisks indicate significant differences ($P < 0.01$) using bimodal test with the response probability for the duration of rest. (**e**) Averaged wrist torque (flexion, $n = 28$ trials; extension, $n = 24$). (**f**) Mean EMGs (FCU, $n = 28$; ECU, $n = 24$). Polarity of ECU EMG was inverted for consistency with torque. Gray shading indicates the intervals over which the PSTHs in **a**–**c** were calculated.

intraspinal stimuli delivered near the site of recording. Typical results from Monkey M (**Fig. 6**) were obtained at the site of an interneuron whose short-latency SR responses were reduced during active movement (**Fig. 6a**). The average antidromic volleys in the cuff evoked by stimuli at the recording site were larger during active movement than during rest in both flexion and extension trials, indicating increased PAD during active movement. The peak-to-peak amplitude (**Fig. 6c**, see arrows in **Fig. 6b**) and area (**Fig. 6d**) of the antidromic response were largest during active flexion and extension movements compared to all other behavioral epochs. At a site of another first-order interneuron (**Fig. 6e**), the excitability was tested using different stimulus currents. The plot of peak-to-peak amplitude of the antidromic response was shifted to the left during active movement, indicating that afferent terminals were depolarized. These data suggest that PAD occurred at the same time that monosynaptic responses of interneurons were reduced.

DISCUSSION

Together, our observations provide direct evidence that presynaptic inhibition suppresses some cutaneous input to the spinal cord in a behaviorally dependent manner during normal voluntary movements. The monosynaptic responses in active first-order interneurons are reduced simultaneously with increased excitability of the relevant afferent terminals, a combination that implicates presynaptic inhibition. It should be noted that presynaptic inhibition can also occur without PAD (*e.g.*, inhibition mediated by G-protein coupled $GABA_B$ receptor[16], and shunting produced by increased chloride conductance during the activation of GABAergic synapses[9]). These

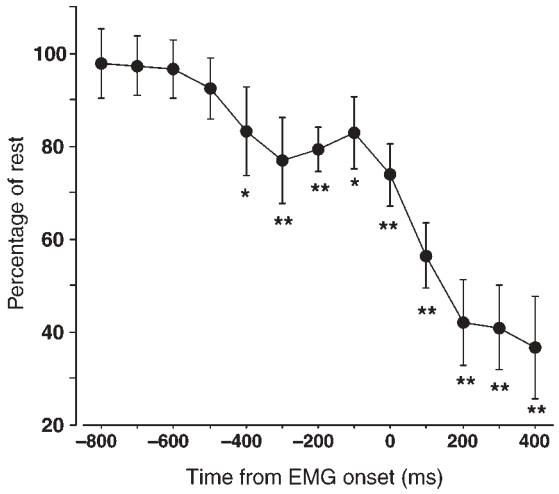

Figure 5 Suppression of SR-evoked response before ENG onset. Summary of 14 interneurons that showed a reduction of responsiveness to SR stimulation prior to EMG onset. Averages (± s.e.m.) of peak area of PSTHs compiled from different intervals relative to EMG onset ($n = 14$) shown as a percentage of area during rest period. Asterisks indicate significant differences compared to rest using a Wilcoxon signed ranks test (*$P < 0.05$; **$P < 0.01$).

additional presynaptic mechanisms could further account for the reduced monosynaptic responses.

The major sources of presynaptic inhibition are peripheral inputs from afferent fibers and central commands in descending pathways. Peripherally evoked presynaptic inhibition in cutaneous afferents arises primarily from other cutaneous afferents, and partly from secondary muscle spindle and tendon organ afferents[9,15,28,30], which are activated during both active and passive movements[31]. Presynaptic inhibition of afferents can also be evoked from cerebral cortex and brainstem[12,32,33]. Descending commands generating ramp-and-hold wrist movement are typically phasic-tonic, beginning before EMG activity onset[34], and are relatively less active during passive movement[35], consistent with the absence of EMG activity during passive movement (**Fig. 2c**). Our observations that a partial suppression of evoked responses occurs preferentially during active movements and precedes EMG onset point to a dominant role for descending motor commands in generating the presynaptic inhibition of cutaneous afferents, as compared to peripheral feedback that results from movement. PAD could also be generated by accumulated potassium in the extracellular space[36], but a recent study suggests that this mechanism has only a minor role, at least for cutaneous afferents[37].

The fact that the afferent input was inhibited presynaptically indicates that the CNS reduces self-induced input at the earliest

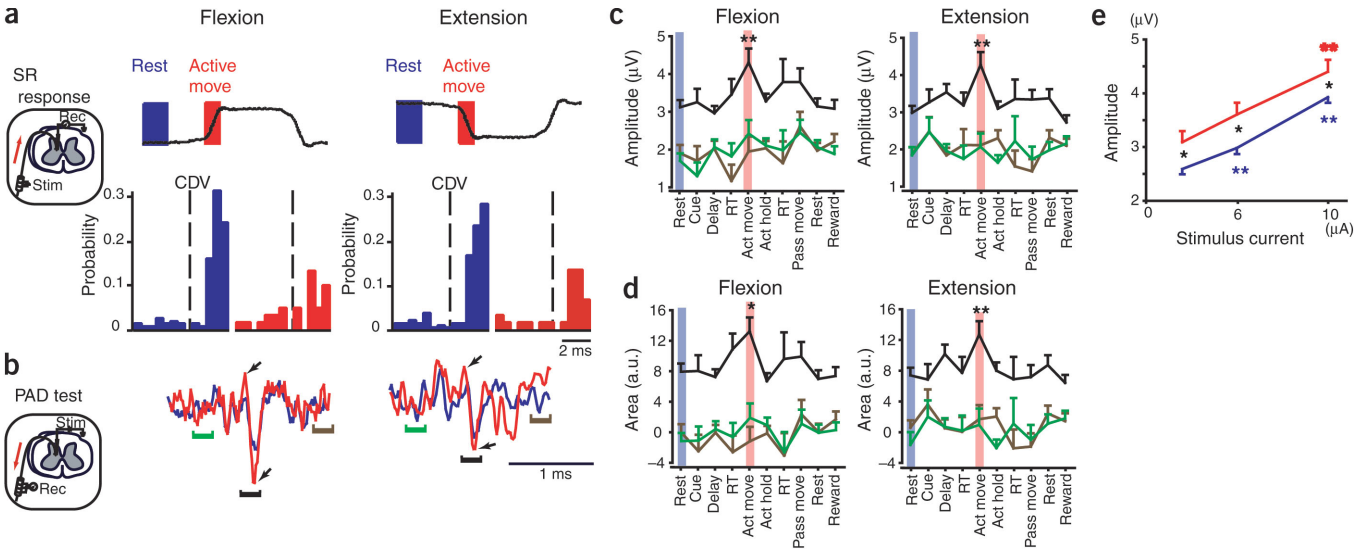

Figure 6 Excitability testing of SR afferents. (**a**) Reduction in SR-evoked responses in interneurons is shown by PSTHs during rest (blue) and active movement (red) periods of flexion (left: $n = 155$ and 60) and extension (right: $n = 176$ and 58) trials in monkey M. SR stimulus intensity was 2.1 times threshold for the incoming volley. Dashed line shows time of CDV. During active movement, mean firing rate increased significantly (flexion, from 29 to 51 spikes/s; extension, from 29 to 46 spikes/s) and peak area of the evoked response decreased significantly (flexion, from 0.68 to 0.20; extension, from 0.65 to 0.27). (**b**) Averaged antidromic volleys evoked by microstimulation at site of the interneuron during rest (blue) and active movement (red) periods for flexion (left, $n = 171$ and 46) and extension (right, $n = 193$ and 56) trials. All traces are aligned to stimulus onset. Stimulus intensity was 10 μA and remained constant throughout recording. The larger evoked volleys during active movements (arrows) reflect a larger number of afferent fibers recruited and/or an increased probability of activating individual axons, both resulting from enhanced PAD of SR terminals. Horizontal bars below the record indicate the intervals over which the area of antidromic volley (black) and that of two baseline samples before (green) or after (brown) the antidromic volley were calculated. (**c**) Peak-to-peak amplitude (mean ± s.e.m.) of antidromic volleys (black) and that of two baselines before (green) or after (brown) the antidromic volley in each behavioral epoch (see Methods). Asterisks indicate significant differences compared to rest ($P < 0.01$). No statistical differences compared to rest were found for the two baselines. (**d**) Areas (mean ± s.e.m.) of antidromic volleys and that of two baselines in each behavioral epoch. *$P < 0.05$, **$P < 0.01$ (compared to rest). There were no statistical differences between rest and the two baselines. (**e**) Peak-to-peak amplitude (mean ± s.e.m.) of antidromic responses to different stimulus currents at another intraspinal site where a first-order interneuron was recorded. Rest (blue) and active move (red) combines flexion and extension trials (2 μA, $n = 380$ and 147; 5 μA, $n = 281$ and 115; 10 μA, $n = 382$ and 136). Asterisks indicate significant differences compared to the response evoked by 2 μA (red and blue) or differences between active movement and rest (black; *$P < 0.05$; **$P < 0.01$).

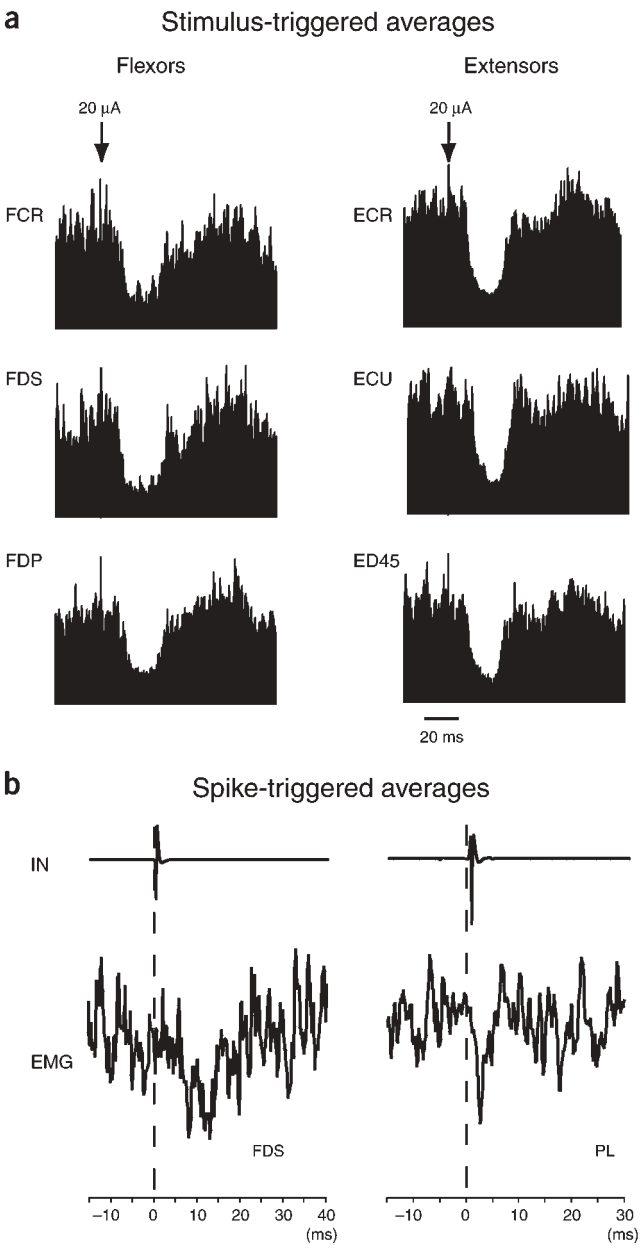

Figure 7 Suppression of muscle activity evoked from site of interneuron recording. (**a**) Post-stimulus suppression of rectified muscle activity in stimulus-triggered averages aligned with single microstimuli (20 μA; 522 pulses) delivered at the site of a first-order relay neuron in the C7 segment. Arrow indicates stimulus time. Activity of all recorded muscles was transiently suppressed. (**b**) Spike-triggered averages of rectified muscle activity, showing post-spike suppression from first-order interneurons. Left, suppression of FDP by interneuron located between C7 and C8 (13,748 sweeps); right, suppression of PL by C8 interneuron (1,182 sweeps). FCR, flexor carpi radialis; FDS, flexor digitorum superficialis; FDP, flexor digitorum profundis; ECR, extensor carpi radialis; ECU, extensor carpi ulnaris; ED45, extensor digitorum digiti 4,5; PL, palmaris longus.

possible stage. In contrast, postsynaptic inhibition of these neurons would reduce their responsiveness in a relatively nonspecific way. Interestingly, most, but not all, first-order interneurons showed reduced responses to cutaneous input during movement. This is consistent with the known specificity of presynaptic inhibition for particular afferents[30,38,39]. It may also suggest that descending systems can preferentially reduce specific peripheral inputs that might interfere with a descending command, and thereby maintain greater control of spinal circuits during voluntary movement. Although we found no differential characteristics of cells whose input was modulated, it would be interesting to investigate other functional properties, such as projections.

These findings have several functional implications, depending on the projections of these interneurons. The activity of the relay neurons can contribute both to spinal circuitry generating movement[1] and to postsynaptic ascending pathways[2], so this inhibition could have motor and sensory consequences.

The segmental motor consequences can be inferred from the muscle responses evoked by electrical microstimulation within the spinal cord. Intraspinal stimulation at sites of first-order interneurons typically produced strong inhibition (13/16) of task-related EMG in flexor and extensor muscles, as seen in **Figure 7a.** Thus, output from these sites, which probably reflects the effects of the recorded first-order interneurons and afferent fibers, would reduce ongoing muscle activity. This result is consistent with the known inhibitory effects of cutaneous reflexes on muscle activity[40,41]. In fact, for 11/38 interneurons, spike-triggered averages of EMG[25,34] confirmed directly that these interneurons produced post-spike suppression (**Fig. 7b**). The suppression of these interneuron responses would therefore aid movement generation, as sensory-evoked activation of these interneurons during movement would produce unpredictable inhibition of agonist motorneurons and impede activation of agonist muscles. The dorsum of the monkey's hand was always in contact with the hand-holder, so presynaptic inhibition would help suppress the inappropriate reflex inhibition of agonists by attenuating input from cutaneous afferents. Thus, presynaptic inhibition of peripheral input during active movement makes functional sense. Moreover, the lack of presynaptic inhibition during the passive movement is also functionally appropriate, as muscle activity is absent during this phase.

Previous studies found that the stimulation of cutaneous pathways[42] and dorsal horn interneurons[43] can have both excitatory and inhibitory actions on cat hindlimb motor neurons. Cutaneous afferents had predominantly inhibitory effects in slow-twitch motor units and excitatory effects in fast-twitch motor units in the anesthetized cat[42] and awake human subjects[44]. In our behavioral task, the low levels of wrist torque were probably generated largely by slow-twitch motor units. This could explain why our stimulus- and spike-triggered averages revealed predominantly inhibitory effects (compare to ref. 41).

The sensory consequences of the observed inhibition would arise from contributions of these interneurons to ascending pathways, such as postsynaptic axons in the dorsal columns[45–48] and spinothalamic pathways[2]. During active movements, the perceived intensities of cutaneous stimuli are decreased[6] and perceptual thresholds increased[5]. Moreover, the cortical potentials evoked by cutaneous stimulation are reduced during[3] and before[4] movement. We also observed that the amplitudes of field potentials evoked in primary somatosensory cortex by SR stimulation are modulated in parallel with the responses of the first-order interneurons (data not shown). Of course, these cortical effects could also be mediated by modulation of the direct dorsal column pathway. Primary afferents ending in the cuneate nucleus also undergo presynaptic inhibition evoked from cortex and periphery[12], which may turn out to be similarly modulated with behavior. Further modulation may occur at other relay sites and within cortical circuits. In any case, the present results indicate that

presynaptic inhibition could have an important role in these psychophysical and physiological phenomena.

In summary, we report direct evidence that presynaptic inhibition modulates cutaneous input to the primate spinal cord preferentially during normal voluntary movements. Thus, the central commands initiating movement are accompanied by a reduction of self-induced inputs that could counteract the movement and potentially interfere with accurate control. This presynaptic inhibition also contributes to the increased psychophysical thresholds observed during movement. Similar mechanisms may operate at relays of other sensory modalities during normal behaviors.

METHODS

Subjects. We obtained data from two male *Macaca nemestrina* monkeys (K and M). Experiments were approved by the Institutional Animal Care and Use Committee at the University of Washington. During training and recording sessions, the monkeys sat upright in a primate chair with the right arm restrained and elbow bent at 90°. The hand was held in a cast with the fingers extended and the wrist in the mid-supination/pronation position. The left arm was restrained loosely.

Surgical implant. After training, surgeries were performed aseptically with the animals under 1–1.5% isoflurane anesthesia. Head stabilization lugs were cemented to the skull with dental acrylic and anchored to the bone via screws. A stainless steel recording chamber was implanted over a hemilaminectomy in the lower cervical vertebrae[25]. Bipolar electromyographic electrodes were implanted subcutaneously in 10–12 forearm muscles. Two cuff electrodes were implanted on the SR nerve: a distal bipolar cuff for stimulation (midway between elbow and wrist) and a tripolar cuff for recording volleys (4–5 cm proximal to the bipolar cuff). The threshold current to evoke an afferent volley (115 ± 14 μA) and the volleys evoked by a given intensity were stable throughout the behavioral epochs.

Recording procedure. During recording sessions, the head and vertebral implants were secured to the primate chair and a microdrive was attached to the chamber via an X–Y positioning stage. Activity of neurons in the C6-T1 segments was recorded extracellularly with tungsten microelectrodes while the monkey performed wrist flexion and extension movements in an instructed delay task. The SR nerve was stimulated at 3 Hz during recording sessions, and units with short-latency evoked responses were studied selectively. For testing the modulation of interneuron responses, stimulus current was adjusted so that the probability of evoking a response during task performance was approximately 50%. The segmental response latency was calculated relative to the incoming volley recorded in the cord dorsum potential (CDP) in some recording tracks. We adopted a central latency of less than 1.5 ms as a criterion for monosynaptic linkage, consistent with previous evidence[49,50]. Immediately after recording SR-evoked responses for some interneurons, we carried out excitability testing[15] without moving the electrode. Intraspinal microstimuli (0.1-ms bipolar pulses, 3–10 Hz, 3–30 μA) were delivered through the microelectrode during task performance, and antidromic compound action potentials were recorded by the proximal SR cuff electrode and then averaged (**Fig. 6**).

Measurements of antidromic volleys. The sizes of the antidromic volleys in the SR nerve evoked by intraspinal microstimulation were evaluated in terms of their peak-to-peak amplitudes and areas. The bins with maximal (peak) and minimal (trough) amplitudes were first identified from a comprehensive average of the antidromic volleys compiled for all stimuli and all behavioral epochs. This averaged volley was also used to identify the onset and offset bin of the volley, and an inflection bin between its peak and trough, for measurement of the area. The inflection bin was defined by the time that the average waveform crossed the baseline mean, as determined by the average value from 10 to 5 ms before the intraspinal stimulus. These bins were then used to measure the amplitudes and areas of the individual volleys evoked by each stimulus. Peak-to-peak amplitude was measured as the difference between the maximal value in three adjacent bins around the peak bin and the minimal value of three adjacent bins around the trough bin. This measure was used to deal with sampling jitter in individual records. Area was measured by summing the values of each bin from onset to inflection and from inflection to offset, and subtracting the latter from the former. For statistical comparison, amplitude and area were also measured for two baseline intervals before and after the average volley (**Fig. 6b**) using procedures and bins with relative spacing identical to those used for the volleys. For each behavioral epoch, the amplitudes and areas of antidromic volleys and baselines were statistically compared using an unpaired *t*-test.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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