Activity-dependent changes in intrinsic excitability of human spinal motoneurones produced by natural activity

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Rossi A, Rossi S, Ginanneschi F. Activity-dependent changes in intrinsic excitability of human spinal motoneurones produced by natural activity. J Neurophysiol 108: 2473–2480, 2012. First published August 29, 2012; doi:10.1152/jn.00477.2012.—The current study was designed to evaluate activity-dependent changes intrinsic to the spinal motoneurones (MNs) associated with sustained contractions. The excitability of spinal MNs (reflected by the antidromically evoked F-wave) innervating the abductor digiti minimi muscle (ADM) was measured in 12 healthy subjects following maximum voluntary contractions (MVCs) of ADM lasting 5 s, 15 s, 30 s, and 60 s. Upon cessation of the contractions, F-waves showed a depression, which increased in depth and duration with increasing duration of contraction. Following a 5-s contraction, there was a 20% decrease, which waned in 2 min, whereas a 60-s contraction produced a 40% decrease and waned in over 15 min. The changes in excitability of peripheral motor axons produced by the MVCs were measured by recording an ADM compound muscle action potential (CMAP) of ~50% of maximum to a constant ulnar nerve electrical stimulation. On cessation of the contractions, there was a prominent decrease in size of the CMAP; following a 5-s MVC, it produced a 10% decrease in the size of the test CMAP, which recovered in 2 min, whereas following a 60-s MVC, it produced a 30% decrease, which recovered in over 15 min. Statistical analysis (correntropy) showed a high-order mutual dependence between F-wave and CMAP, and both were significantly dependent on MVC duration. Because of the parallel excitability changes in peripheral axons and spinal MNs, our interpretation is that intrinsic excitability of the axon initial segment (i.e., where the action potential is generated) and peripheral axon segments changed in a similar, activity-dependent manner.

Axon initial segment; F-wave; motor axons

The output of all neurons critically depends on the interaction between synaptic strength and intrinsic properties. It is commonly assumed that changes in synaptic efficacy are both necessary and sufficient to account for adaptive neural behavior. However, there is growing evidence that neuronal activity itself modifies not only synaptic efficacy but also the intrinsic excitability, i.e., the propensity of a neuron to fire action potentials when exposed to an input signal (Schulz 2006). In fact, the intrinsic excitability of neurons is responsible for the translation of synaptic input into the particular output function of a given neuron (Marder et al. 1996; Zhang and Linden 2003). The intrinsic excitability of a given neuron is roughly matched by the synaptic activity of the neural network in which the neurons are embedded (Beranec et al. 2007; Beranec and Straka 2011; Pfanzelt et al. 2008; Rössert et al. 2011; Rössert and Straka 2011; Smith and Perrier 2006). In other words, the ongoing levels and patterns of electrical activity can modify the intrinsic excitability of neurons, resulting in experience-dependent changes. Activity-dependent plasticity is common in the developing brain and during behavioral tasks in adult animals, and it is assumed to play an important role in memory, learning, and compensatory phenomena (Beranec and Idoux 2012; Fan et al. 2006; Grubb and Burrow 2010a, b; Li and Baccini 2012; Saar and Barkai 2003). Activity can also play a role in a variety of short-term adaptive mechanisms, resulting from slowly activating and inactivating membrane conductance, which makes the response of a neuron dependent on its recent history of activity. The intrinsic adaptation of the firing frequency of cat spinal motoneurones (MNs) after many consecutive spikes (Kernell and Monster 1982a, b) is an example of ongoing processes that use activity to regulate the intrinsic properties of neurons. In fact, spinal MNs may manifest various intrinsic adaptive behaviors. In addition to bistability (i.e., their membrane can be set to different states of excitability) (Kiehn and Eken 1997; Schwindt and Crill 1995), intrinsic properties of MNs are shown to play an important role in shaping the pattern of synaptic drive to produce rhythmic output in model MNs (Wright and Calabrese 2011). Also, Hyngstrom et al. (2007) demonstrated that small-joint ankle rotations modified (by reducing membrane-persistent inward currents) the intrinsic properties of ankle extensor MNs in the cat.

In humans, even relatively brief contractions can produce a significant increase in the threshold of peripheral motor axons due to activity-dependent membrane hyperpolarization (Kiernan et al. 2004; Kuwabara et al. 2002; Vagg et al. 1998). It has been hypothesized that a similar activity-dependent decrease in intrinsic excitability could also involve the spinal MN pool, thus reducing the output to a given synaptic input (Butler and Thomas 2003; Giesebercht et al. 2011; Johnson et al. 2004; McNeil et al. 2011; Racinais et al. 2007; Rossi et al. 2010). However, this hypothesis remains to be proven.

The present study was designed to ascertain whether the excitability of a human spinal MN pool is subject to activity-dependent changes compatible with changes intrinsic to MN. Furthermore, we verified whether their motor axons exhibited parallel changes in excitability. Excitability of the spinal MN pool innervating abductor digiti minimi muscle (ADM) was tested by analyzing their backfiring discharges (F-waves) following antidromic activation by supramaximal electrical stimulation of the ulnar nerve, applied before and after 5, 15, 30, and 60 s of maximum voluntary contractions (MVCs) of ADM. Studies on cat lumbar sacral MNs indicate that F-waves are produced by backfiring discharges of a proportion of spinal MNs following antidromic activation of their peripheral axons and that this is due to...
re-excitation of the axon initial segment (Coombs et al. 1957; Eccles 1955; Lloyd 1943; Renshaw 1941). F-wave occurs when the membrane potential allows the antidromically activated spike in the axon initial segment to spread to the MN, producing a somatodendritic spike with a timing sufficiently delayed so that its peak occurs after the refractory period of the axon initial segment. A decrease in membrane excitability at the axon initial segment may prevent F-wave generation either by blocking the antidromic potential transmission or by preventing re-activation of the axon trigger zone. On the other hand, membrane hyperpolarization at the body cell may depress the somatodendritic spike and therefore, prevent F-wave generation. Facilitation of MNs, i.e., axosomatic membrane depolarization, favors invasion of the cell soma by the antidromic spike; however, if this occurs too rapidly, residual axonal refractoriness may prevent propagation of the resulting orthodromic action potential. This suggests that F-waves could be better suited to detect inhibition than facilitation of MNs (Lin and Floeter 2004).

Excitability of the distal motor axon segments innervating the ADM (i.e., axons of the ADM spinal motor nucleus) was assessed by measuring the size of the direct compound muscle action potential (CMAP) 50% of maximum evoked by a constant weak electrical stimulus to the ulnar nerve applied before and after 5, 15, 30, and 60 s of MVC of ADM.

Our main results are that: 1) natural activity resulted in a long-lasting (min) depression of MN excitability; 2) the depth and duration of this depression depended on the duration of the ongoing electrical activity; and 3) excitability of the spinal MN pool depressed in parallel with that of their peripheral motor axons.

METHODS

General Procedure

Twenty healthy human subjects (five females and seven males; age range, 25–55 yr) were studied. The procedures were approved by the local ethics committee, and the studies were conducted according to the Declaration of Helsinki. The experimental design was an adaptation of that described in detail elsewhere (Rossi et al. 2010). Subjects reclined on a dental chair with the right arm oriented in a horizontal plane: the shoulder abducted at 45°, the elbow flexed to 110°, and the wrist joint in neutral position at 0°. Forearm and hand were immobilized in prone position. The first four fingers were secured to a rigid hand piece, whereas the fifth finger was placed at ~10° horizontal abduction and secured to a strain gauge sensor to provide secure mechanical coupling between the digit and the transducer. Special care was taken to prevent any change of position of the wrist and finger joints during ADM contractions. Each experiment was repeated at least two times on each subject, including two of the authors. Mechanical and myoelectric responses to motor axon stimulation were recorded from ADM.

Force Recording

The force produced by the contraction of the right ADM was measured with a linear strain gauge (FSG Sensors & Instrumentation, Les Clayes Sous Bois, France). The subjects performed maximal isometric voluntary abdution of the little finger against resistance (strain gauge). Maximal contractions were used to ensure that all relevant MNs innervating the ADM were activated at higher firing rates (note that in this muscle, the relative contribution of rate coding is greater than motor-unit recruitment to force production during MVC) (Gelli et al. 2007). Ongoing target force was displayed on an oscilloscope in front of the subject. The data were collected at a sampling rate of 1,000 Hz for force tracings (Del Santo et al. 2007).

Stimulation and Recording Procedures

Responses were evoked (Grass S88X stimulator) and recorded (Tektronix TDS3000C) using Spike 2.0 software, version 4.01 (Cambridge Electronic Design, Cambridge, UK). All electrodes were adhesive silver/silver chloride electrodes, 15 × 20 mm (Spes Medica SRL, Milan, Italy). Recording electrodes were placed over the ADM muscle—the negative one on the belly of the motor point of the muscle and the reference one 2 cm apart over the muscle. Stimulation electrodes were placed 2 cm apart over the ulnar nerve at the wrist. The skin under the stimulating and recording electrodes was carefully prepared with abrasive paste. Hand and forearm skin temperature was maintained above 32°C by an infrared lamp.

CMAPs were evoked in ADM by electrical stimuli to the ulnar nerve (single rectangular pulses of 0.5-ms duration) delivered by a constant current stimulator at random intervals (1–5 s each). F-waves were evoked in the ADM MNs by supramaximal stimulation applied to the ulnar nerve at the wrist. The stability of the stimulus (duration: 0.3 ms; intensity: 20% above that required to evoke the maximal CMAP) was verified by monitoring the direct muscle potential; special attention was paid to check that the size and shape of direct muscle response before and after MVCs were identical (see example in Fig. 1). Only experiments on which this precondition was obtained were accepted. F-wave persistence, i.e., the number of measurable F-waves divided by the number of stimuli, was deter-
mired offline from a series of 10 successive stimuli. To distinguish F-waves from background noise, the recorded EMG signal was reviewed visually; only appropriately timed deflections, which clearly contrasted with the baseline noise, were accepted as F-waves. The smallest accepted F-wave amplitude varied between 30 μV and 50 μV. The area of each individual F-wave was measured, and then, the average F-wave area was calculated for each recording series. EMG data of 100-ms duration recorded over the ADM after each stimulus were filtered (filter settings: 3 kHz low-pass filter; 20 Hz high-pass filter) and then digitized at a sampling rate of 5 kHz.

**Experimental Protocol**

Three different studies were performed on each subject. Each experiment session included recordings of muscle responses (CMAPs or F-waves) before and after a single MVC. The latter lasted 5 s, 15 s, 30 s, or 60 s. The subject relaxed upon instruction, and electrical stimulation started 5 s after the MVC ceased. Given that each contraction generated some level of fatigue, the same subject could not perform more than one contraction on the same day. Stimuli were then applied in a fully randomized sequence with intensity for eliciting a CMAP of 0.1 mV (baseline-negative peak) was established. Wrist and its position adjusted until the site with the lowest threshold of this size: 50% of the maximum before contraction and then kept constant over the entire study period. Two main reasons motivated the choice of this size: 1) it corresponded to the segment of the input-output curve most sensitive to the effect of contraction (see Fig. 3), and 2) it was plausible that most of motor units recruited in the F-wave are also recruited in the CMAP 50% of the maximum.

**Peripheral Input-Output Relationship**

In all subjects, performance of a voluntary contraction reduced the excitability of motor axons. Figure 3 shows the input-output curves elicited by stimulation at the wrist before and after MVC. This relationship had a sigmoid shape with a bottom value reflecting activation of the most excitable axons, a slope indicating input-output recruitment efficiency, and a top value reflecting activation of the entire pool of motor units (virtually 100%) recruited by maximum stimulation (Fig. 3, A–D). Absolute bottom and top values of the postcontraction input-output curves were the same as in control, although the latter required higher stimulus intensity: following 60-s MVC, the intensity required to obtain a maximum CMAP was 1.7 times higher than control. Top values of the curve in percent of control values were 99.9 ± 0.08, 99.45 ± 0.45, 100 ± 0.12, and 99.45 ± 0.22 for 5-, 15-, 30-, and 60-s contractions. Maximum CMAPs in mV were 9.32 ± 0.4, 9.8 ± 0.36, 9.9 ± 0.3, and 9.38 ± 0.3 (control: 9.4 ± 0.4) for 5-, 15-, 30-, and 60-s MVCs.

**Analysis and Statistics**

Unless otherwise indicated, the results are given as the means ± SE. Statistical significance was set at the 5% level. In addition to Pearson’s coefficient of correlation, we computed the correntropy coefficient as a further measure of correlation. The correntropy coefficient is able to characterize both higher-order relationships and nonlinearity between interacting systems, and it is assumed to be a measure of dependence between variables [conveyed either by a linear or a nonlinear relationship; see Prince (2010) for a review]. Since the correntropy coefficient produces a nonzero value for two dependent random variables, a Kruskal-Wallis test was used to verify this hypothesis. Finally, a Mann-Whitney U-test was used to compare the effects of contraction on CMAP and F-wave series.

**RESULTS**

During the sustained MVC lasting 5, 15, 30, and 60 s, average force (in Newton) was 8.62 ± 0.15, 8.01 ± 0.16, 7.42 ± 0.13, and 5.93 ± 0.19, i.e., 96.0%, 87.0%, 80.5%, and 64.5% with respect to the initial level (9.2 ± 0.58; Fig. 2).

![Fig. 2. Average force at 5, 15, 30, and 60 s of maximal isometric abduction of the 5th finger in 12 subjects. Left vertical axis: force expressed in Newton (N). Right vertical axis: force normalized (%) to the 1st s of contraction. Each box is the average of 5 s of the recording (i.e., the last 5 s for the 15-, 30-, and 60-s MVCs).](http://jn.physiology.org/doi/10.1152/jn.00477.2012)
Slope value of the of the Boltzmann function, fitted to experimental data, decreased progressively with increasing MVC duration: values were 0.29 ± 0.002, 0.30 ± 0.01, 0.37 ± 0.005, and 0.60 ± 0.01 (note that for mathematical reasons, the slope of the Boltzmann equation is expressed as 1/slope) for 5-, 15-, 30-, and 60-s contractions, respectively.

Figure 3, a–d, shows the difference between pre- and postcontraction input-output curves (baseline = control curves). The curves exhibited a decay phase (peaking at intensity 2.10 and 2.20 × MTh after 5- and 60-s MVCs, respectively), followed by a rising phase reaching the maximum at intensity 3 and 5 × MTh after 5- and 60-s MVCs, respectively.

It is of interest to note that the stimulus intensity 2 × MTh separated two phases of the input-output relationship: a first, fast-rising phase, followed by a second, slow phase. This was also apparent in control curves (Fig. 3, A–D): average slope value of the first phase (below 2 × MTh) was 80.64 ± 1.42; average slope value of the second phase (above 2 × MTh) was 19.72 ± 2.27. Slope values were obtained by fitting two linear regressions to points from 1 to 2 × MTh and from 2 to 3 × MTh, respectively (the latter intensity value corresponded to that required to obtain maximum CMAP in control condition).

**Time Course of Postcontraction Changes in the F-wave**

Following a maximal voluntary effort, the F-wave to the antidromic activation of ADM MNs decreased. As with the CMAP, the reduction of the F-wave was greater the longer the contraction was, with both a higher peak depression and a slower return to control levels (Figs. 4, E–H, and 5). The average peaks were 80.0%, 68.0%, 63.0%, and 54.0% for 5-, 15-, 30-, and 60-s contractions, respectively (Fig. 5A); it took 1.30, 3.60, 9.50, and 16.6 min for the test CMAP to recover to control levels (these values corresponded to the interpolation of a second-order regression fitted to the experimental data with the horizontal control line; Fig. 5B).

F-wave depression following contraction was not due to a decrease in the frequency of the response occurrence: pre- and postcontraction values were 98.3 ± 6.3 and 96.7 ± 7.9, respectively. Obviously, the total number of MNs giving a backfiring response (i.e., the size of F-wave) depends on the frequency of the response occurrence in individual neurons following their antidromic invasion.
The extent and duration of depression of the test CMAP and F-wave significantly covaried with the duration of contractions. Pearson’s coefficient of correlation between CMAP and F-wave sequences showed a high-order correlation ($P < 0.0001$). To further verify the mutual dependence between CMAP and F-wave series, we computed the coefficient of correntropy. CMAP vs. F-wave amplitude $0.45 \pm 0.005$; CMAP vs. F-wave recovery time $0.50 \pm 0.006$. All pairs of variables were significantly nonzero (Kruskal-Wallis test; $P < 0.0001$), i.e., far from conditions of independence between variables.

To provide an overall comparison of the effects of contraction on CMAP and F-wave, we computed the area under curves in Fig. 4, A–H [$y = f(x)$ between $x = 0$ and $x =$ recovery value; baseline = control value]. F-wave areas were 28.5, 53.0, 175, and 490; CMAP areas were 14.0, 16.0, 70.5, and 300 for 5-, 15-, 30-, and 60-s contractions. The F-wave exhibited a significantly (Mann-Whitney U-test = 5.0; $P = 0.385$) larger overall postcontraction decrease than CMAP.

**DISCUSSION**

The present study has provided evidence that natural activity can produce a significant decrease in the excitability of human spinal MNs, which increase in depth and duration as the duration of the contraction increases. In particular, prolonged voluntary activity of the ADM caused a prominent activity-dependent depression in excitability of its MNs, measured as antidromically evoked F-wave discharge: following 5-s MVC, it produced a 20% decrease, which waned in 2 min, whereas 60-s MVC produced an ~40% decrease, waning over 15 min.

A similar activity-dependent depression in excitability (reflected by the test CMAP) was observed in the peripheral motor axons innervating the ADM: following 5-s MVC, it produced a 10% decrease in the size of the test CMAP, which recovered in 2 min, whereas following a 60-s MVC, it produced a 30% decrease, which recovered in over 15 min. In fact,
there are known activity-dependent changes in human motor axonal excitability with voluntary activity (Kiernan et al. 2004; Kuwabara et al. 2002; Rossi et al. 2010; Vagg et al. 1998), and such changes were confirmed by the present study.

Comparison of the F-wave with the test CMAP indicated that activity-dependent changes in excitability at the MN soma or axon initial segment (see below) paralleled those of distal axonal segments (see Fig. 4). Second-order statistics (Pearson’s coefficient) showed a high-order correlation between CMAP and F-wave series. Their mutual dependence was confirmed by the analysis of correntropy, i.e., by a non-Gaussian and nonlinear signal processing (Liu et al. 2006).

This activity-dependent decrease in excitability, which occurs in MNs following a voluntary contraction, has never been documented previously, and comparison with the change in motor axons has not been undertaken. These issues will be discussed below, together with the rationale for the conclusion that hypoexcitability was due to changes intrinsic to the MN.

Methodological Considerations

Before considering the mechanisms held to be responsible for the interdependence of F-wave and CMAP, some technical and measurement issues need to be discussed. The stability of the experimental condition before and following different MVCs among subjects is a crucial point. This was verified by analyzing the effects of MVCs on the relationship between the stimulus intensity applied to the ulnar motor axons and the size of evoked ADM response (input-output curves in Fig. 3). Following each contraction (from 5 s to 60 s), the relationship did not change their general shape: maximum depressive effect of contractions was constantly observed on CMAP size evoked by stimulus intensity $2 \times \text{MTH}$, whereas above this value, the depressive effect progressively decreased until the size of CMAP reached the same top control value. As shown in Fig. 3, a–d, descending and ascending limbs of the relationship (reflecting the extent of the activity-dependent depression on CMAP size from minimum to maximum) remained stable (but for magnitude) following different MVCs. These findings allow for a further consideration. Since the activity-dependent hypoexcitability that occurs in motor axons increases with increasing firing rates and train duration (Kiernan et al. 2004), it could be expected that the extent of hypoexcitability was inhomogeneously distributed among axons. Indeed, although firing rates elicited by a MVC could not generate a fully fused tetanus in all motor units (Macefield et al. 1996), the slower the motor unit, the lower its frequency is (Bellemare et al. 1983). By analysis of the input-output curve, the maximum depression following each contraction was observed with a CMAP size of 50–70% of maximum. This could suggest that smaller axons, innervating slower motor units of the ADM, were activated mainly by stimuli above $2 \times \text{MTH}$. Although different morphological factors other than input impedance can influence recruitment of the axons by transcutaneous electrical stimulation (Feiereisen et al. 1997), it is nonetheless plausible that the upper, slow-rising phase of the input-output curve mainly reflected activation of the motor units innervated by small, low-threshold spinal MNs innervating smaller motor units of ADM. If so, this increases confidence that most motor units recruited in the F-wave were also recruited in the test CMAP (50% of the maximum). Indeed, because of the collision in motor axons, F-waves cannot occur in small MNs that discharge reflexively in response to the maximal group Ia afferent volley set up by the supramaximal ulnar nerve stimulus (Mazzocchio et al. 1995). This strengthens the reliability of the results arising from comparison between F-wave and CMAP series.

Finally, the fact that the top value of the input-output curves reached the same value as in control (although at progressive higher stimulus intensity with increasing contraction durations) demonstrated that all motor axons could still be activated after voluntary activity; i.e., the activity-dependent hypoexcitability was overcome by supramaximal electrical stimulation. In fact, axonal hypoexcitability reflects an increase in threshold to electrical stimulation due to membrane hyperpolarization occurring in motor axons when they conduct trains of impulses (Bostock and Grafe 1985). Moreover, axonal hyperpolarization has no effect on action potential propagation along the axon (Kuwabara et al. 2002), except at regions where the safety margin for conduction is physiologically low (see below). It follows that the observed changes in F-wave could not be due to decrease in size (or increase in desynchronization) of the antidromic volley responsible for the MN-backfiring discharge.

Origin of MN Depression

The reduction in MN excitability could occur because of persistent synaptic inhibition of the MN membrane. This possibility seems improbable. First, it seems unlikely that sources of synaptic inhibition arising, for example, from the muscle receptors in relation to the state of contraction (group Ib or group III and IV spinal pathways) or from MN recurrent collaterals (Renshaw cells) may last minutes after the contraction has ceased. Moreover, there is evidence suggesting a lack of recurrent inhibition in the motor nuclei of the intrinsic hand muscles (Mattei et al. 2003). Second, activity-dependent depression in excitability of MNs innervating hand muscles (as tested by F-wave technique) has also been observed after sustained antidromic activation of the spinal motor pool in spinal cord-injured subjects (Butler and Thomas 2003). There-
fore, it seems plausible to conclude that depression of the F-wave following MVCS reflected an activity-dependent change intrinsic to the MN. Although this change was recorded after the end of contraction, nevertheless, it must develop early during activity; indeed, depression was evident after very short contractions (5-s MVC). Therefore, the activity-dependent changes in intrinsic MN excitability should not be seen as an aftereffect of MN activity.

In the present study, the depression in MN excitability matched the time course of the depression of their distal axonal segments. The most immediate interpretation is that the same activity-dependent depression observed in the distal segment of the axon also involved its initial segment. As mentioned in INTRODUCTION, membrane hyperpolarization at the axon initial segment (i.e., the specialized region near the start of the axon where clusters of sodium channels generate the action potential) (Coombs et al. 1957; Foust et al. 2010; Kole et al. 2008; Meeks and Mennerick 2007; Palmer and Stuart 2006) can contribute to the decrease in F-waves. This does not imply that the mechanism responsible for changing excitability at distal and proximal (initial) axonal segments was similar. Evidence exists that sustained activity may depress the initial axon segment membrane excitability via activation of serotonergic receptors (Perrier and Cotel 2008), whereas the same activity may cause peripheral axon membrane hyperpolarization via activation of the electrogenic sodium-potassium pump (Bostock and Grafe 1985). Depression of initial axon segment excitability may prevent generation of the MN response to its antidromic activation either by blocking the antidromic potential or by blocking the backfiring orthodromic potential waves.

1) Because of the low safety factor for transmission at the axon initial segment (especially in the transition from the medullated to the nonmedullated axon and at the large expansion of the membrane surface that occurs as the axon flares out to the soma-dendritic membrane) (Eccles 1955), membrane hypoxcitability at this level may cause conduction block of the test antidromic volley (Coombs et al. 1957). This can reduce the size of soma-dendritic spike and therefore, the probability of the MN backfiring. 2) Even assuming that the antidromic volley could reach the MN soma, because of the hypoxcitability at the axon initial segment, the antidromically induced soma-dendritic spike would not in any way be sufficient for generating a backfiring action potential.

In addition to changes at the initial axon segment, F-wave depression could result from hypoxcitability at soma-dendritic membrane level. Under this condition, the antidromically evoked soma-dendritic spike is expected to be too small to discharge the MN. A decrease in soma-dendritic membrane excitability could be caused by back-propagating spikes occurring when a cell generates action potentials. Indeed, evidence exists that back-propagating action potentials may result in an activity-dependent decrease in overall cell excitability (Fan et al. 2006).

Conclusions

The present findings show that human spinal MNs are subjected to activity-dependent inhibition, likely due to a reduction in their intrinsic excitability. Based on the evidence that the depression in excitability of the spinal MN pool correlated with that of their peripheral axons, it seems reasonable to conclude that the peripheral motor axon and axon initial segment properties change in a similar manner. If excitability of the axon initial segment (i.e., the source of a nerve impulse) is reduced, any given input (reflex or voluntary) would have a reduced capacity to activate the MNs. As hypothesized by McNeil et al. (2011) and Sawczuk et al. (1995), changes in intrinsic MN excitability caused by repetitive discharge could be a predominant mechanism contributing to the reduction in responsiveness of MNs during sustained maximal effort. This possibility should be considered seriously since although progress has been made in the study of muscle fatigue (Enoka and Duchateau 2008; Gandevia 2001), we are still unable to specify the mechanism responsible for spinal MN impairment during fatiguing contractions.

As a corollary, the evidence that activity shapes the intrinsic excitability of MNs might reflect a more distributed property of human neurons. If so, in addition to the aforementioned adaptive phenomenon during fatigue, the activity dependence of neuronal intrinsic properties could play an important role in learning and memory. Actually, they arise through activity-dependent modifications of neural circuit (see INTRODUCTION).

NOTE ADDED IN PROOF

The activity-dependent changes in excitability of human MNs have also been documented in a paper published online as an Article in Press by the Journal of Physiology (Khan SI, Giesebrecht S, Gandevia SC, Taylor JL). Activity-dependent depression of the recurrent discharge of human motoneurones after maximal voluntary contractions. J Physiol 2012, Aug 20, Epub ahead of print).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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