Mechanisms and functional implications of motoneuron adaptations to increased physical activity

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Abstract

Motoneurons demonstrate adaptations in their physiological properties to alterations in chronic activity levels. The most consistent change that appears to result from endurance-type exercise training is the reduced excitatory current required to initiate and maintain rhythmic firing. While the precise mechanisms through which these neurons adapt to activity are currently unknown, evidence exists that adaptation may involve alterations in the expression of genes that code for membrane receptors which can influence the responses of neurons to transmitters during activation. The influence of these adaptations may also extend to the resting condition, where ambient levels of neuroactive substances may influence ion conductances at rest, and thus result in the activation or inhibition of specific ion conductances that underlie the measurements of increased excitability that have been reported for motoneurons in the anesthetised state. We have applied motoneuron excitability and muscle unit contractile changes with endurance training to a mathematical computerised model of motor unit recruitment (Heckman and Binder, 1991). The results from the modelling exercise demonstrate increased task efficiency at relative levels of effort during a submaximal contraction. The physiological impact that nerve and muscle adaptations have on the neuromuscular system during standardized tasks seem to fit with reported changes in motor unit behaviour in trained human subjects.

Key Words: motoneuron, motor unit, endurance training, exercise, recruitment
Introduction

We now have converging evidence from different experiments and laboratories that motoneurons change in their functional properties with chronic increases and decreases in regular physical activity (Beaumont and Gardiner 2002, 2003; Gardiner et al. 2006; Krutki et al. 2015; Krutki et al. 2017). The mechanisms by which these adaptations occur have not been elucidated, although consideration of possible mechanisms has been presented and discussed previously (Gardiner et al. 2006).

In this brief review, we attempt to revisit this issue, with the addition of experimental results that have been reported recently. Specifically, our goal is to provide a more fulsome discussion of the effects of increased and decreased activity on motoneuron properties, our current view as to mechanisms for adaptations, and application of experimental results to a model of motor unit recruitment (Heckman and Binder 1991) in order to get some idea as to the practical implications of these adaptations.

Motoneuron biophysical properties demonstrate plasticity across the physical activity spectrum

Table 1 constitutes a summary of the experimental results for effects of various levels of physical activity on properties of rat alpha-motoneurons. Interventions include models of reduced activity, such as spinal cord transection in the thoracic region, which will render motoneurons hypo-active due to interruption of descending tracts and thus voluntary activation, and removal of weight-bearing via suspension of the hindlimbs for 4 weeks. Models of increased activity include chronic access to voluntary exercise wheels, intense daily endurance treadmill training, two hours per day, for up to 16 weeks, daily weight-lifting training for 5 weeks, and compensatory muscle overload achieved by tenotomy of synergistic muscles, for up to 12 weeks. We believe that the “control” condition in these experiments, which was housing rats individually in small standard rodent cages, is most likely a model of extreme sedentary behaviour, similar to an individual confined to a small living space with no possibilities for physical activity, and that the true control condition against which comparisons should be made is actually
the voluntary wheel access condition. In the latter, rats are able to choose their level of daily activity, and
this varies considerably among animals, much as is the case in humans. Nonetheless, comparisons of
increased and decreased use effects are made in Table 1 using this ultra-sedentary “control” group.

There are several general conclusions that we can arrive at in examining the data in Table 1:

1. **A minimal level of daily voluntary activity has significant effects on several motoneuron properties.** This is evident in considering the significant changes noted in Table 1 in motoneurons of rats given access to exercise in voluntary wheels. From these data, it is evident that sedentary life-style impacts motoneurons by decreasing their excitability through depolarization of both the membrane potential and voltage threshold (which represents the mean membrane voltage at which sodium channels open during depolarization towards an action potential). In addition, the decrease in the amplitude of the spike afterhyperpolarization (AHP), which may influence rhythmic firing properties, is affected in “sedentary” motoneurons. As one might expect, these changes occur in those motoneurons that are most frequently used when one is moving around at a low to moderate intensity (“slow” motoneurons), as is the case with voluntary wheel activity.

2. **For some properties, there is a continuum adaptation between complete inactivity and dramatically increased activity.** For example, voltage threshold becomes depolarized with reduced activity, and hyperpolarized with increased activity. In the latter, the “fast” motoneurons, which show a dramatic increase in recruitment with intense treadmill training, are preferentially affected (since in voluntary wheel activity, only slow are affected, whereas in endurance training, both slow and fast are affected). Interestingly, “fast” motoneurons are also preferentially targeted for adaptation in the condition of hindlimb suspension – perhaps the weight of the hindlimb and the non-weight-bearing movements that occur in this condition are sufficient to maintain “slow” motoneuron voltage threshold. This property is important in determining the amount of excitatory current necessary to evoke an action potential – a
depolarization and hyperpolarization of the voltage threshold renders the cell less and more excitable, respectively. Similarly, spike AHP amplitude and cell capacitance tend to decrease and increase with reduced and increased activity, respectively. Rheobase current (current intensity evoking a single spike) and the current necessary to evoke a rhythmic discharge tend to increase and decrease with low and high activity levels, respectively, reflecting in part the changes in voltage threshold.

Different types of increased physical activity may have differing effects on motoneuron properties. The exercises shown in Table 1 include daily intense treadmill endurance training (2 hours per day, 5 days per week, 16 to 20 weeks), resistance-type training (1 hour per day, 5 days per week, 5 weeks), and compensatory overload of the medial gastrocnemius (12 weeks), achieved by tenotomy of its synergists. The latter is a form of chronic muscle overload which induces changes in muscle fiber composition towards a slow phenotype (Krutki et al. 2015), and can thus be considered an extreme increase in physical activity. With exception of medial gastrocnemius synergist tenotomy, which substantially increases the workload of the medial gastrocnemius muscle, the volume of exercise and physiological response is comparable to humans engaged in endurance (i.e. marathon running) and resistance exercise.

Some biophysical properties show similar adaptations to all three types of increased activity, including spike rise time (which decreases) and minimum current threshold for rhythmic firing (which also decreases). Thus, the ion conductances that govern these processes (primarily sodium and potassium conductances) are quite plastic to even relatively short periods of increased activity (such as the shorter, more intense episodes of neuromuscular activity that one would see with resistance exercise, compared to prolonged endurance training). Although it appears that only “fast” motoneurons are impacted for these two properties, it is necessary to point out that motoneuron “type” was not distinguished in the intense endurance training experiment, and these properties were not measured in the voluntary wheel exercise condition – thus, all of these conditions (intense treadmill training, resistance training, and
compensatory hypertrophy) may have experienced similar decreases in these two parameters, occurring primarily in fast motoneurons.

Other intrinsic motoneuron property adaptations were specific to the type of chronic physical activity increase. For example, compensatory hypertrophy evokes an increase in input resistance and therefore excitability of fast motoneurons, which may indicate either a decrease in the membrane surface area of the cell body and proximal dendrites, and/or a change in the passive conductances which modulate this property. It is worth noting that slow motoneurons tend to have larger input resistance per unit cell surface area (Kernell and Zwaagstra 1981), thus suggesting that, in the case of extreme increase in endurance-type physical activity characteristic of the compensatory overload model, some fast motoneurons may be transitioning to a more “slow-like” phenotype. The increase in AHP amplitude in this model is also consistent with this interpretation – slow motoneurons have larger-amplitude AHPs.

Interestingly, motoneurons of endurance-trained rats undergo adaptations which do not occur with resistance-type training and compensatory overload. These include hyperpolarization of the resting membrane potential and a decrease in the slope of the steady-state frequency/current relationship (which actually increases with resistance-type training). This implies that the mechanisms to control motor output are different between the two exercises and that motoneurons adapt differently to different activity modes.

Spinal cord transection is more than merely reduced activity for motoneurons below the lesion. The motoneurons below a complete spinal cord injury show adaptations that are quite different from reduced activity alone. This is not unexpected, as the spinal cord transection model deprives the motoneuron not only of voluntary activation patterns, but also of monoamines and other factors which influence motoneuron properties (Reckling et al. 2000). Removal of supraspinal influence results in changes in the expression of receptors and ion channels, and in the development of spasticity, all of which are not
merely activity-related (Chopek et al. 2015). Thus, motoneurons distal to a complete spinal cord transection show changes in rhythmic firing characteristics (reduced slope of the frequency/current relationship, minimum rhythmic firing frequency, and minimum current necessary for rhythmic firing) which do not occur with reduced activity (cage confinement, non-weight-bearing). That the physiologic changes between reduced activity and eliminated activity are different suggests that the mechanisms governing intrinsic property modification are different from those that are sedentary versus those that have a complete spinal cord injury.

Mechanisms for motoneuron adaptations to altered physical activity

All of these changes are due to altered ion conductances, which can take the form of changes in the number and/or location of ion channels and receptors, and/or changes in their modulation. Several attempts have been made to model these biophysical changes by changing conductances in a 5-compartment model rat motoneuron with 10 active conductances (Dai et al., 2002), with some success (Gardiner et al. 2006). For example, increase in sodium conductance seems to play a major role in explaining training-induced adaptations, with possible contributions from leak conductances (ions moving down their electrochemical gradient via non-gated channels). On the other hand, decreased sodium conductance alone had significant predictive value for the changes induced in motoneurons by hindlimb suspension (Cormery et al. 2005).

We set out to attempt to determine if there were changes in the proteins underlying these conductance changes (Woodrow et al. 2013) using laser capture microdissection of lumbar alpha-motoneurons combined with quantitative PCR to measure the expression of a multitude of gene products. We decided on measuring the mRNA levels for a sizeable array of specific, known to be major contributor, ion channels, receptors, neurotrophins, and growth-related proteins, in samples of motoneurons harvested from spinal cord sections. While the measurement of protein vs mRNA would
be preferred, there are several advantages to the latter, if the limitations of these measurements are recognized. Changes in mRNA content as an expression of increased gene expression are isolated to the cell soma, and can be amplified in order to be measured, whereas subtle increase in the content and/or distribution of motoneuronal proteins would be difficult to measure, especially those that become localised in dendrites and axon initial segment.

We found that changes were quite modest, and did not include the expression of ion channels, including those for Na+ conductance changes discussed above. Rather, the most significant changes in expression we have previously reported (Woodrow et al. 2013) included decreased expression of a subunit of the GABA receptor, the metabotropic glutamate receptor (mGluR), and the serotonin receptor 5HT1A. These proteins are involved in tonic inhibition and mediate their effects via ambient GABA, glutamate and serotonin. For example, extrasynaptic GABA-A receptors in motoneurons can be activated by ambient GABA, activating a tonic shunt that, via modulation of chloride channels, decreases input resistance, increases rheobase, affects action potential properties such as depolarization of the voltage threshold and slowing of the speed of action potential generation, and shifts the position of the frequency-current relationship to the right, all of which indicate decreased excitability (Canto-Bustos et al. 2017). Similarly for mGluR, in mouse motoneurons, activation of this receptor, via activation of a mixed cation shunt, depolarizes the RMP, decreases input resistance, depolarizes the voltage threshold for action potential generation, and also decreases the amplitude of locomotor bursts during evoked locomotor activity. mGluR activation also caused a decreased firing frequency response to the same current – a right shift of the frequency/current relationship – and a reduced height and rate of rise of action potentials (Iwagaki N and Miles 2011). As for the decreased 5HT1A receptor expression, tonic activation via ambient serotonin could act to inhibit action potential generation at the initial segment, where these receptors appear to be located (Perrier JF 2016; Perrier et al. 2017). The effects that parallel decreases in expression of these three proteins alone can exert on motoneuron properties...
measured in an anesthetized preparation emphasize the complexity of how a single protein can have a dramatic effect on several properties. Further to this, the futility of attempting to ascribe change in a physiological property to a single protein is palpable.

It is interesting to note that GABA receptors co-localise with mGluR that are involved in neural responses of synaptic plasticity and learning in rat cerebellar Purkinje cells (Tabata and Kano 2010). In the H-reflex conditioning experiments of Wolpaw and colleagues, increase and decrease in expression of GABA receptors occur in monkey motoneurons following down-conditioning and up-conditioning respectively, in motoneurons, and in other neurons in the spinal cord (Wang et al. 2006, 2009; Pillai et al. 2008). Thus, it is conceivable that a mechanism for exercise training-induced plasticity in spinal neurons includes the regulation of expression of receptors such as those referred to above, and we are currently focusing our attention in that direction.

**Importance of physical activity-related adaptations to performance.**

It is important to stress that the adaptations summarized in Table 1 are in neurons in anesthetized rats. We have attempted to address this by examining many of these properties in a decerebrate rat preparation, in which anesthetics are gradually removed, and in which locomotor-like activity, normally suppressed by many anesthetics, can be evoked via brainstem stimulation (MacDonell et al. 2015). Thus, motoneurons are more “awake” then when anesthetized (“asleep”). These “awake” motoneurons demonstrate changes in several of their properties when changing from a state of rest to a state of locomotor activity, including AHP amplitude (decreases), rheobase current (decreases), voltage threshold (hyperpolarizes), slope of the frequency/current relationship (decreases and leftward shift), and spike frequency adaptation (eliminated). Interestingly, many of these are the same properties that show changes in “sleeping” motoneurons after exercise training, and often in the same direction. Since these changes with onset of locomotor activity in “awake” motoneurons are similar to the changes seen
with training in “sleeping” motoneurons, this suggests that perhaps “sleeping” motoneurons at rest in endurance-trained rats are closer to a “readiness for activity” or "primed" state. In this, sensitivity of the nervous system is increased or in elevated state of readiness and this may occur through changes in the content of receptors that are activated during locomotion. Our plans to measure “awake” motoneuron properties before and during evoked locomotor activity, in rats previously subjected to alterations in chronic activity, will answer this question.

Do endurance-trained motoneurons become more like slow motoneurons?

Do motoneurons, like their innervated muscles, take on more slow-like properties after chronic endurance training? It does not appear so. We recently measured gene expression of several proteins in motoneurons which innervate a slow (soleus) and fast (lateral gastrocnemius) muscle. Fast and slow motoneurons differ in the expression of a variety of proteins that are significant for function, including 5HT1A receptor, muscarinic cholinergic receptor 2, potassium channel KV2.1, voltage-sensitive calcium channel CaV1.3 (all lower in S); mGluRI, small potassium channel SK3, synaptic vesicular protein SV2A, and the tropomyosin receptor kinase C (TrkC) (all higher in slow type motoneurons). 5HT1A receptor expression which is decreased after endurance training is also lower in slow motoneurons – however, mGluRI, which was decreased after endurance training, is significantly higher in slow motoneurons (unpublished observations). The GABA-A subunit which was also decreased with endurance training is similar in expression in slow and fast motoneurons. Thus, as is the case with muscle tissue, complete conversion from “fast” to “slow” phenotype does not occur with intense endurance training.

A model to demonstrate the potential benefit of motoneuron adaptations on performance

A way to visualise the impact of motoneuron and muscle unit changes on neuromuscular performance is to apply the several documented adaptations to a model of motor unit recruitment. The
following presents modifications to the original Heckman and Binder (1991) motor unit model describing
discharge rate, recruitment and force characteristics for a pool of 100 MG motor units, in response to
varying magnitudes of synaptic excitation (input). While the original parameters employed in the model
utilized experimental data collected from cats, a modified version presented by Webber et al. (2009)
integrated observations collected from humans to describe potential changes in neuromuscular
performance as a result of reported changes to quadriceps motor units in ageing. In the iteration
presented below, adaptations to the model are based on changes documented at the neuron level (see
Table 1) and at the level of the muscle unit, in response to endurance training. Wherever possible,
human data was relied upon; however, animal data was used to provide insight that cannot be gained
using human participants. The control or untrained condition utilized the model parameters presented
in Webber et al. (2009). Results from the model are shown in Figure 1 and Figure 2.

The model contains eight parameters that describe: 1) the amount of excitatory current
required to recruit each motor unit (Ithres); 2) the slope of the primary range of motoneuron firing (G1);
3) the slope of the secondary range of motoneuron firing (G2); 4) frequency of motoneuron discharge at
recruitment (fthresh); 5) frequency of the motoneuron discharge at the point of transition between the
primary and secondary range (ftrans); 6) maximum tetanic force of the recruited muscle fibers in
Newtons (Fmax); 7) twitch force as a fraction of Fmax, termed F-start; 8) a constant that relates the
frequency of motoneuron firing to the contractile response of the muscle unit fibers (Tf); and 8) a
constant that transforms the shape of the force/frequency function to a sigmoidal output (P). The
model permits one to apply a current input to the system, and to demonstrate the motoneuron, motor
unit and whole-muscle responses to that input. Complete model parameters for untrained human
motor units have been published previously (Webber et al. 2009) and for more information, readers are
directed to the original Heckman-Binder model (Heckman and Binder 1991).
A limited amount of information exists regarding physiological changes in the mechanical and discharge characteristics of motor units following endurance training but available research suggests that current threshold at recruitment, minimal frequency of sustained discharge (Beaumont and Gardiner 2002; 2003; MacDonell et al. 2012), motor unit recruitment range, initial firing rates, and average firing rates (Adam et al. 1998) are all decreased following endurance training. In addition, there is evidence to suggest that unloaded shortening velocity of single fibers may be increased with endurance training (Malisoux et al. 2007; Harber and Trappe 2008), an effect which might be isolated to the low-threshold motor units only (Schluter et al. 1994; Widrick et al. 1996; Trappe et al. 2006). At the alpha-motoneuron (MN) level, reported changes include a hyperpolarized voltage threshold for action potential generation (Vth) (Beaumont and Gardiner 2003), a reduction in spike frequency adaptation (the time dependent decrease in discharge rate during prolonged depolarizing current injection), and reduced minimal motoneuron discharge rates and depolarizing current levels for motoneuron rhythmic firing (MacDonell et al. 2012) following endurance training in rat hind-limb motoneurons. Compared to untrained motor units in humans, trained motor units display decreased initial and sustained motor unit firing rates (Adam et al. 1998; Vila-Cha et al. 2010), increased number of active motor units over a larger force range at similar percentages of maximal voluntary contraction (MVC) and the resulting force produced during these isometric contractions also show less variation (i.e. increased steadiness) (Adam et al. 1998). Despite the adaptations noted above, maximal muscle force (Vila-Cha et al., 2010; Mettler and Griffin 2016) and whole muscle twitch mechanical properties do not appear to be affected by endurance training (Grosset et al. 2009) in humans. While conflicting reports exist as to whether the rate of whole muscle tension development increases or stays the same after training (Grosset et al. 2009; Vila-Cha et al. 2010; Mettler and Griffin 2016), the maximal velocity of individual muscle fibers during unloaded shortening has been shown to increase for Type I muscle fibers following endurance training (Schluter et al. 1994; Widrick et al. 1996; Trappe et al. 2006).
Model Alterations

**Ithres**: The level of excitation needed to activate motoneurons is reflected by the amount of synaptic current needed for action potential generation. Given reductions in Vth and current level needed to sustain rhythmic firing, the parameter Ithres was reduced linearly by 20% across the motoneuron pool. The extent to which Ithres was reduced was chosen for several reasons, 1) Vth decreases (Beaumont and Gardiner, 2003) between 13 – 17% for rat fast and slow MNs, respectively, following endurance training; 2) minimum current used for rhythmic MN discharge is decreased by 32 % (MacDonell et al. 2012) in endurance trained rats 3) recruitment force in Newtons (N) was 26% lower (Adam et al. 1998) in motor units of the first dorsal interosseous (FDI) of the dominant hand (trained) in humans, which implies a reduction in current threshold in at least some motor units.

**fthresh**: The firing rate at recruitment for rhythmic firing is represented by fthresh in the model and was reduced by 15% for all motor units. Records from hind-limb motoneurons also support reduced minimum discharge rates by as much as 30% in endurance trained rats (MacDonell et al., 2012). In trained motor units of the human FDI, an 11% decrease in initial firing has been shown (Adam et al. 1998).

**F-end**: The percentage of maximal muscle unit force generated at the end of the primary range of motoneuron firing is represented by the constant F-end. It was decided to use primary and secondary ranges of motoneuron firing, even though these properties have not been demonstrated in human motoneurons. In untrained human quadriceps (Webber et al. 2009) a value of 0.8 (i.e. 80% of maximal force is developed at the end of the primary range) was left unchanged from Heckman and Binder model (1991). One way to alter the rate of force generation is to alter F-end. In the Trained motor unit model, this value was reduced to 0.75.

**Tf and P**: Tf and P are parameters that change the "fastness" (the amount of normalized force achieved at a given discharge rate) of the muscle, by altering the left-right position of the force/frequency curve.
and altering the shape of the sigmoidal nature of this relationship. These values change quasi-linearly from the lowest-threshold (MU-1) to the highest-threshold (MU-100) motor unit, assuming that motor units become gradually faster-contracting through this threshold range. The literature suggests that endurance training impacts the fastness of the muscle, especially in lower threshold motor units (Schluter et al. 1994; Widrick et al. 1996; Trappe et al. 2006). To change the fastness of the muscle in lower threshold motor units, the values for Tf and P for the 25th motor unit (MU-25) were shifted to MU-1 in the endurance trained model, while the Tf and P values for MU-100 were unchanged. Linear interpolation between the new MU-1 and original MU-100 was used to fill in the values for the other motor units. This ensured the impact was maximized for the lower threshold motor units (see Figure 2B).

Changes to the model that reflect neuromuscular adaptations resulting from endurance training result in earlier motor unit recruitment at any level of synaptic drive, reduced firing rates of earlier recruited motor units, and a speeding of the low-threshold muscle units favouring the production of less force for any given frequency. These changes are illustrated in Figure 1A, where the target whole-muscle force is 20% of MVC. Note that more motor units are recruited to provide the same whole-muscle force, forces of individual motor units are lower, frequencies of firing are generally lower, and the total excitatory current necessary to produce the force is approximately 10% less. This motor unit pool is therefore more excitable – possibly via a hyperpolarized motoneuron voltage threshold – and is recruited earlier over a wider range of forces than an untrained motor unit pool.

These adaptations, through a decrease in force output by recruited motor units, addition of higher threshold motor units to “share” the required force, and reduced firing frequencies, may contribute to a reduction in central fatigue and peripheral fatigue that promote the increased time to fatigue noted in endurance athletes, during submaximal contractions. The lower frequencies may also delay the gradual depolarization of membrane potential during sustained firing that would tend to
reduce excitability over time. In exercising humans, motoneurons lose excitability during a maintained submaximal contraction (McNeil et al. 2011). It is noteworthy that, even at 80% of MVC, firing frequencies are reduced in the endurance-trained model (Figure 1C).

Furthermore, the idea that the level of descending drive from higher brain centers may lead to activation of inhibitory 5-HT1A receptors at the axonal hillock due to spill over of serotonin is an attractive hypothesis for a mechanism of central fatigue (Perrier 2016; Perrier et al. 2017). If this is the case, the reduced level of synaptic drive required to run the motor neuron pool at submaximal intensities may lead to a reduction of motoneuron inhibition as a part of central fatigue (see Figure 1A & 1B and Figure 2A). The results achieved by the motor unit model have been shown in a variety of individual studies. In humans, decreases in mean motor unit steady-state discharge have been shown during isometric contractions at 30% of maximal force (Adam et al. 1998; Villa-Cha et al. 2010); initial discharge rates at recruitment are also lower, as is recruitment threshold (Adam et al. 1998).

Figure 2 illustrates that motor units in the endurance trained motor units are recruited earlier (Panel A, upper), and have a more gradual force production (Panel B, upper) than untrained motor units (Panel A & B, lower), particularly for the lower-threshold motor units. In addition, Figure 2A shows that for any given synaptic input, firing rates are faster in trained motoneurons. Coupled earlier with the observation of earlier recruitment, endurance training produces a motor unit pool that is more excitable and develops force over a broader range of synaptic input. To tie this back to the observations noted above in previous studies, the mechanisms potentially behind this shift include hyperpolarized voltage threshold for action potential generation, increased recruitment at lower levels of synaptic drive and a slowing of the muscle, whereby forces are generated slower and over a larger range.

The model did not incorporate changes in total muscle force as a function of endurance training because there is not clear agreement in the literature on this subject. Fink et al. (1977) reported that elite endurance trained athletes had increased slow twitch muscle fiber area (20%) compared to
untrained individuals, but showed no difference between "good" endurance athletes and untrained individuals. To complicate matters, Vila-Cha et al. (2010) showed no change to maximal voluntary contraction (MVC) in endurance trained individuals, while Mettler and Griffin (2016) showed both a training effect and an increased MVC in endurance-trained subjects. Further to this, Ereline et al. (2011) reported no change to muscle twitch forces for flexors or extensor after endurance training. With exception of elite athletes, it is likely that maximal muscle force is not impacted in a major way by endurance training, and therefore does not impact the results of the model.

Important Aspects of Neuromuscular Physiology Not Included in the Model

This model examines a single output for a motor unit pool in response to synaptic input. An aspect that is not considered is repeated prolonged input of varying and constant intensity.

Persistent inward currents (PICs): In motoneurons, PICS are largely located in the dendritic tree and help amplify synaptic input by allowing a prolonged depolarizing current to enter the cell, thereby increasing the gain or frequency-current relationship (see review Heckman et al. 2008). PICs are generated by two ionic conductances: a long-lasting Ca++ conductance that takes longer to develop but is also active for longer and a Na+ conductance that activates and deactivates more rapidly. PICs are increased in the presences of monoamines, and are thought to be especially important initiating and driving long-lasting rhythmic firing (Heckman et al., 2008). Also, PICs likely reduce the time-dependent decay in discharge rate associated with spike frequency adaptation (see below). Since PICs have been shown to be larger in lower threshold motor units (Heckman et al. 2008), the result of the adding these conductances to the model may increase the amplitude of PICs across the motor unit pool, and thus reduce the amount of synaptic input need to rhythmically active higher threshold motor units in the endurance trained state. In spite of obvious implications for changes in PICs as a result of increased or decreased activity, this information is not currently available.
Spike frequency Adaptation: Spike frequency adaptation is the time-dependent decrease in discharge rate during sustained synaptic input (Granit et al. 1963). In endurance trained rats, SFA was shown to be reduced by comparing the instantaneous frequency of the mean of the last three intervals to the first interval during a 500-ms depolarizing pulse. The training-induced decrease in SFA would be expected to impact the model in two ways. First, in a sustained isometric contraction, additional motor unit recruitment to maintain constant whole-muscle force would be expected to occur more slowly, due to the relatively higher maintenance of firing frequencies of firing motor units in the trained state. In addition, due to the lower initial frequencies of firing, SFA would be less marked, since SFA occurs more markedly at higher frequencies of firing (Button et al. 2007). During intermittent contractions, such as one would see during running or cycling, the training-induced decrease in SFA might be expected to slow the gradual increased recruitment that is necessary to maintain muscle force. SFA also occurs during intermittent stimulation (Spielmann et al. 1993), although there is a possibility that SFA does not even occur in “awake” motoneurons during locomotor-like activity (Brownstone et al. 2011; MacDonell et al. 2015).

Maximal Firing and Inhibitory Influences: Motoneurons have limits to the peak discharge rate. The model does not provide any mechanism to plateau motoneuron firing rate. In addition, inhibitory influence in general is lacking in the model, which may be important after training. For instance, one of the mechanisms that may be at work following endurance training is reduced overall inhibition of the motoneuron at the soma, which may be due to changes in GABA mRNA levels (Woodrow et al. 2013) that potentially lead to decreased protein synthesis.

Interneurons: The motor unit model seeks to explain how motoneuron excitation, behaviour and muscle unit response to input for a motor unit pool; however, it must be kept in mind that adaptation to motor output may very well include other components of the locomotor circuitry within the spinal cord.
While interneurons have never been tested as a mechanism for spinal motoneuron plasticity, it remains a viable alternative as an additional possible site of adaptations to endurance training.

Continuous versus time-varied synaptic input: Motoneurons engaged in a rhythmic task like locomotion display relatively large changes to many intrinsic motoneuron properties. The AHP is reduced, even in preparation of locomotion, Vth is hyperpolarized acutely for all motoneurons in the rat and a majority of motor units in the cat, and spike frequency adaptation is largely reduced. As such, it is possible that varied synaptic input such as that which one might see during locomotor activities reduces the associations between the motoneuron and its muscle unit to a degree that requires a whole new set of parameters to be included in modelling.

Conclusion

Changes in physical activity lead to changes in intrinsic motoneuron properties that impact how motoneurons respond to stimuli. Ultimately neuronal adaptations that occur with endurance training increase the systems readiness to respond with less effort. While the specific mechanism(s) remains to be elucidated, the functional implications of the changes reviewed above lead to a system that achieves submaximal force more effectively. The model used to illustrate changes in motor unit function implies that endurance trained motor units share more of the work with less synaptic drive.

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Conflict of Interest

The authors have no conflicts of interest to report.

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* slow motoneurons only  
** fast motoneurons only  
nm = not measured  
nc = no change  
Imin rf = threshold current for rhythmic firing  
HLS = hindlimb suspension  
SFA = spike frequency adaptation  
SSFF = steady-state firing frequency
Table Captions


Figure captions

Figure 1. Motor unit relative force, frequency and whole muscle force output in endurance trained and untrained human quadriceps. Panel A and B includes absolute (left y-axis) and relative (right y-axis) forces produced for a representative pool of 100 motor units at 20% (panel A) and 80% (panel B) of maximal isometric muscle force (circle: untrained motor units; triangle: endurance trained motor units) and Panel C depicts the firing rates achieved at those forces. Panel D shows the absolute force generated as a function of synaptic input for untrained motor units (solid line) and trained motor units (dashed line); the dashed box represents the data depicted in the inset, illustrating endurance trained motor units are recruited earlier. The data suggest endurance trained motor units are recruited earlier and are active over a greater range of force with lower firing rates at both 20% and 80% of maximal muscle force.

Figure 2. Motoneuron and muscle unit input and output relationships. Panel A shows the motoneuron frequency-current relationship for Endurance Trained (upper panel) Untrained (lower panel) and Panel B includes the motor unit normalized force-frequency relationships in Endurance Trained (upper) and Untrained (lower) human quadriceps. Both panels included relationships from MU-1 (labelled far left), MU-25, MU-50, MU-75, and MU-100 (labelled far right). Figure 2 illustrates that motor units in the endurance trained motor units are recruited with less synaptic input (panel A, upper), and have a more gradual force production (Panel B, upper) than untrained motor units (Panel A & B, lower), particularly for the lower-threshold motor units.
A. Force (N) at 20% of Maximum Force

B. Force (N) at 80% of Maximum Force

C. Frequency (Hz)

D. Force (N) with Synaptic Input (nA)