

Principles of Force Gradation in Skeletal Muscles

D. Kernell

Department of Medical Physiology, University of Groningen, Groningen, The Netherlands

ABSTRACT

A brief survey is given of how motoneurons and motor units are used for the gradation of muscle force during motor behavior. Basic properties of motoneurons and muscle fibers, including major kinds of functional specialization along the axis of 'fast' vs. 'slow', are reviewed. The principles underlying the rate and recruitment gradation of force are described, stressing that the properties of motoneurons and muscle fibers are matched to automate important aspects of the gradation procedure. Recent investigations concerning synaptically evoked changes in the discharge properties of motoneurons receive special attention, including 'plateau' currents and, under appropriate conditions, self-sustained 'plateau' discharges.

KEYWORDS

motoneurons, muscle units, recruitment gradation, rate gradation, plateau currents

INTRODUCTION

The deficient coordination of a clumsy child means, purely descriptively, that the child's body is not moving around in the most optimal manner.

Thus, the many muscles involved are not contracting at the most optimal force levels for the motor task. Most of this problem is likely to be caused by dysfunctions of 'high' brain mechanisms (for example, in neocortex, basal ganglia, cerebellum, brainstem). Nevertheless, motor programs and plans at these higher levels have, ultimately, to become shaped into motor behavior via commands to the final common path of the motor system: the motoneurons and the muscle fibers. Thus, whatever the characteristics of the motor behavior, whether clumsy or not, the motor output system is always involved. As a background for further discussions about the mechanisms of motor function and dysfunction, I give here a brief survey of how the output machinery is organized and how it works, at a cellular level and under normal conditions (for general reviews, see Burke, 1981; Henneman & Mendell, 1981; Kernell, 1992; Binder et al., 1996).

WHAT IS CONTROLLED? STRUCTURAL ORGANIZATION OF MOTONEURONS AND MUSCLE FIBERS

Anatomists have enumerated and named several hundred 'muscles' in the body. In fact, from a functional point of view, the number of distinct force-producing units is even larger than it seems from textbooks because many of the anatomical 'muscles' consist of several different portions that exert their forces in different directions. A clear example of this is, for instance, the deltoid muscle at the shoulder joint. The force-generating cells within a muscle are the long and threadlike skeletal

Reprint requests to: D. Kernell, Department of Medical Physiology, University of Groningen, PO Box 196, 9700 AD Groningen, The Netherlands; e-mail: dhkernell@hotmail.com

muscle fibers, which are often around 50 μm thick but several thousand microns long. Each muscle fiber receives innervation from a motoneuron, a specialized nerve cell having its cell body and dendrites inside the central nervous system and sends its axon into the periphery. Inside a target muscle, the motor axon splits up into numerous terminal branches. Thus, a single motoneuron typically makes synaptic contact with many muscle fibers, whereas each single muscle fiber receives innervation from only one motoneuron. A motoneuron with its muscle fibers constitutes one 'motor unit', and the muscle fibers of a motor unit are often also collectively called a 'muscle unit'. Within skeletal muscles, muscle fibers of different units are intermingled.

Muscle fibers normally contract only when excited by their motoneuron. The muscle unit is the smallest fraction of a muscle that can be activated by the central nervous system. Each muscle is controlled by a population of motoneurons, a 'motoneuron pool'. The cell bodies of the motoneurons lie in the ventral horn of the spinal cord or, for those of cranial nerves, within nuclei of the brain stem. In the spinal cord, the motoneurons of single muscles are organized into elongated cell groups.

The axon terminations of a single motoneuron are typically restricted to a single muscle (only a few exceptions from this rule are known; Emonet-Denand et al., 1971; Sekiya et al., 1992) or even, in several known cases, to distinct portions within single muscles (neuromuscular compartments; for example, English & Letbetter, 1982). Thus, central mechanisms are almost always needed for the activation of different muscles together, as required for coordinated motor behavior.

DIFFERENTIATION OF MUSCLE FIBER PROPERTIES IN RELATION TO MOTOR TASKS

An activated muscle produces a force in a shortening direction; muscles are used for pulling

on things, not for pushing. Besides producing movements by means of muscle shortening (concentric contractions), practically all muscles are also used for 'postural' tasks (namely, for stabilizing joints, often near-isometric contractions) and for 'braking' tasks (lengthening or eccentric contractions). Different kinds of motor tasks are associated with different mechanical, metabolic, and circulatory conditions, and different muscle fibers have become specialized accordingly.

The fact that at all muscle fibers are not alike is easily demonstrated by staining a cross-section of a muscle for its contents of various kinds of enzymes or contractile proteins. Using standard procedures for the staining of a constituent of the myosin molecule, the myofibrillar ATPase (mATPase), two main fiber categories are generally clearly revealed, referred to as type I and II (light and dark respectively after alkaline preincubation). Within each single muscle unit, the various muscle fibers typically have very similar physiological and biochemical properties; thus, from this point of view, muscle units tend to be functionally homogeneous. Hence, the muscle units can also be classified as belonging to different functional types.

The results of combined physiological and histochemical studies have demonstrated that type I fibers tend to be slow and highly resistant to fatigue; thus, they can keep up a series of repeated contractions with little loss of force. At the other extreme, type II fibers are fast but more fatigable; typically, this group is subdivided into several subgroups. In experimental physiological studies, Burke's (1981) scheme of unit classification is often used, categorizing the units into the major groups of (a) fast-twitch fatigue-sensitive (FF), (b) fast-twitch fatigue-resistant (FR), and (c) slow-twitch fatigue-resistant (S).

The shortening contractions that we need for the production of movements might have to be performed rapidly and at great power; in these instances muscles can be activated to the extent

that circulation is temporarily rendered ineffective because of pressure on blood vessels from contracting muscle fibers. Correspondingly, the F units are good at rapidly getting energy out of intramuscular glycogen stores, even without immediate access to oxygen.

Postural contractions are often near-isometric and relatively weak but sometimes have to be maintained for very long times, up to hours. Correspondingly, the muscle fibers of S units have a high degree of endurance; they are well provided with enzymes for oxidative metabolism and are also surrounded by many capillaries for the continuous supply of oxygen and fuel and removal of waste products. The 'slowness' of these fibers makes them metabolically cheap to use in long-lasting near-isometric contractions.

GRADATION OF CONTRACTILE FORCE: RATE AND RECRUITMENT CONTROL

Rate gradation of single unit force

The force-producing muscle fibers of our muscles are the so-called 'twitch fibers', activated via the generation of action potentials. Each time an action potential comes along a motor axon, the potential is transmitted across the neuromuscular synapse at all its muscle fibers. Within each muscle fiber, the action potential is propagating all along its length, activating contractile mechanisms.

The contraction caused by a single action potential is referred to as a twitch, the smallest and shortest possible contraction caused by the neuronal activation of a muscle unit. The twitch lasts much longer than the action potential, but it is still too brief for normal motor behavior. Practically all kinds of movements are evoked by trains of repetitive action potentials. If such a train occurs with action potential intervals similar to the twitch duration, we will simply see a repeated series of

twitches. If the action potential rate is increased, the twitches seem to 'summate': they grow into each other and peak force becomes increased. Thus, over a given range of spike-frequencies, an increased action potential rate gives an increased force; this is how force is graded in single muscle fibers and muscle units. Above a given rate, this process saturates. Then the twitches are completely 'fused', and a further increase of action potential rate gives no increase of force.

Muscles react differently under different conditions. Their force production is influenced by muscle length and by shortening velocity. Further, for the same activation pattern, force may increase ('potentiation') or decrease ('fatigue') as a result of after-effects of preceding activity. The rate-gradation of force is also influenced by muscle temperature and by the precise pattern of pulse intervals in the activation train (review: Binder-Macleod, 1992). However, under each set of conditions, the relation between contractile force and stimulation rate ('tension-frequency' or 'T-f' curve) has, as far as we know, essentially the same general shape: a sigmoid curve with a rather narrow frequency-range within which a variation in activation rate also gives an effective alteration of contractile force. This is the frequency range (with some variation, depending on the circumstances) within which motoneurons have to operate for the effective gradation of force in single units. This is also roughly the frequency range within which motoneurons are often actually found to operate. How is this controlled?

Rate modulation of single motoneuronal activity

A single motoneuron receives thousands of synapses from other cells along its extensive dendritic trees. The discharge activity of a motoneuron is controlled by the summed excitatory and inhibitory activity of all these synapses. Each single synapse produces only a very small effect.

For the production of impulse discharges in a motoneuron, many excitatory synapses have to be active more or less simultaneously. If the summed postsynaptic current is sufficiently strong and long-lasting, then the motoneuron reacts by generating a repetitive impulse discharge. This process can be imitated by applying currents of different intensity to a single motoneuron via a microelectrode. In this way, one can determine how the motoneuron translates current intensity into impulse frequency ('frequency-current' or 'f-I' relation). Over an important lower portion of the total frequency-range of a motoneuron, a practically linear relation exists between the discharge rate and current. For a given motoneuron, this linear 'primary range' of discharge corresponds fairly well to the steep portion of the T-f curve for its muscle fibers. Thus, motoneurons have membrane properties that cause them automatically to discharge at rates that are optimal for the gradation of force in their muscle fibers. For such matching, no controlling neuronal machinery is required. The matching also works across the various types of S and F muscle fibers. Because of their intrinsic membrane properties, the motoneurons of S fibers are active within a lower frequency range than that found for motoneurons of F fibers.

Recruitment control in motoneuron populations

So far I have dealt only with the rate gradation of force in single muscle units. Muscles are not run by single motoneurons, however, but rather by populations of often tens or hundreds of motoneurons. Thus, as one might predict, muscle force is also varied by activating smaller or larger numbers of motoneurons. This phenomenon is referred to as the 'recruitment gradation' of force.

Many synaptic inputs to functional populations of motoneurons (for example, those of a single muscle) are organized such that single premoto-

neuronal axons send branches to many (or even to all) motoneurons involved. Thus, an increased incoming excitation will practically always go to a substantial portion of the motoneuron pool simultaneously: if one motoneuron receives excitation, then its 'colleagues' are likely to receive it as well, although possibly in different quantities. For the achievement of a useful recruitment gradation of force, the various motoneurons should not all be activated at the same threshold level of input. This does not easily happen, however, because, due to differences in intrinsic membrane properties, the motoneurons of a single pool differ very much in their electrical excitability. These differences are such that the various types of muscle units tend to be appropriately selected for different motor tasks.

In most studied kinds of voluntary or reflex contractions, the weak, slow, and fatigue-resistant S units are those most easily recruited; these units are very suitable for producing the weak but long-lasting contractions that are necessary for maintaining and controlling posture. The strong, fast, and fatigue-sensitive FF units are recruited at the other end of the threshold range, which seems appropriate as these units are particularly adapted to the production of the high-power but typically relatively short-lasting contractions necessary for driving rapid movements. This recruitment hierarchy—from weak and slow toward stronger and faster units—corresponds to the motoneuronal and motor unit behavior summarized in the term 'size principle' described by Henneman and his colleagues (review: Henneman & Mendell, 1981). Also in this case, the choices are largely made in an automatic manner, depending on the intrinsic excitabilities of the respective motoneurons; no complex neuronal circuitry is needed for generating these basic patterns of motoneuron pool behavior. Until all motoneurons of a pool have become recruited, rate and recruitment gradation tend to be used more or less in parallel.

VARIATIONS IN THE BEHAVIOR OF INDIVIDUAL MOTONEURONS AND MOTONEURON POOLS

So far I have given a textbook-like description of how force is graded in skeletal muscles. The manner in which the basic set of mechanisms is used, however, can change in various ways, depending on the motor task and the history of the system. Much of the current research concerns this flexibility of the motor output machinery. The following are two major aspects:

- a. the recruitment gradation may take place in different ways for different motor tasks because of differences in synaptic distribution across the motoneuron population;
- b. the rate and recruitment gradation characteristics can become modified because of short- or long-term alterations in the functional properties of individual motoneurons.

Variations of motoneuron pool innervation

The ease with which a synaptic input to a functional motoneuron pool may grade motoneuronal recruitment depends on how close to each other the activation thresholds for the motoneurons are lying. If they were close together, then small changes of pool input would cause large variations in recruitment. On the other hand, if the recruitment thresholds were very far apart, then gradation would be difficult and strong synaptic inputs might conceivably fail to recruit the whole motoneuron population. The relative activation thresholds within a motoneuron pool might be markedly altered by synaptic inputs. For instance, if a certain input gave relatively more excitation to intrinsically less excitable motoneurons, then functional recruitment thresholds would come closer together and, hence, the 'recruitment gain' would become increased (Kernell & Hultborn, 1990). Motoneurons receive their synaptic inputs

from many different sources, and it is very likely that the organization of their total input might show a great variation across different motor tasks. Recruitment gain would be altered by variations in synaptic distribution along the axis of S <--> F motoneurons. Several studies in the past have demonstrated the existence of such differences: some systems are biased toward the S or F side of the spectrum, other systems are S vs. F neutral (for examples, Powers & Binder, 2001). Thus, it is highly likely that changes in recruitment gain may indeed take place during the course of normal motor behavior.

A further complication concerns the extent to which the various synaptic command systems are targeted onto whole motoneuron pools. It has long been known that, depending on the motor pattern to be executed, different 'task groups' of units may be preferentially activated within single muscles (Hoffer et al., 1987). Such groups may be localized within topographically different muscle portions, each containing fast as well as slow muscle unit types. Furthermore, this situation might occur also in cases for which contractions of these different muscle portions have very similar mechanical effects—for example, long head of human biceps brachii (ter Haar Romeny et al., 1984), or cat's peroneus longus (Hensbergen & Kernell, 1992). An intriguing question is how such 'task groups' are organized in a multi-muscular context: are the true 'functional' motoneuron pools, for a given synaptic command system, consisting of fractions from the pools of several anatomical muscles, bundled together for specific spatial patterns of muscle coordination?

Changes in the activation properties of individual motoneurons

Recent investigations have revealed two major classes of synaptic influence on motoneuronal discharges:

- a. Excitatory or inhibitory synaptic activation can have the conventionally expected effect of simply producing currents that alter the motoneuronal discharge in accordance with its intrinsic f-I relation. In anesthetized animals, activated synapses mainly provide such 'driving currents'. Thus, there is then often a relatively good agreement between the effects of postsynaptic currents and corresponding intensities of injected currents (Granit et al., 1966; Kernell, 1969; Powers & Binder, 1995, 2000; 2001).
- b. Much research is going on concerning post-synaptic effects of a 'motoneuron-modifying' kind. In this case, synapses do not provide only excitatory or inhibitory currents but also (or mainly) alter the way in which motoneurons respond to driving currents. The best known effect of this kind concerns a modification of motoneuronal membrane properties such that the motoneuron becomes partly 'self-stimulating'. Under such conditions, the motoneuronal membrane becomes sensitized such that it generates a persistent inward current when depolarized above a certain level during a sufficient length of time (Delgado-Lezama & Hounsgaard, 1999; Heckman & Lee, 1999; Hultborn, 1999; cf. Schwandt & Crill, 1980). This self-generated current adds to any synaptically or externally supplied excitation; thus, it will drastically change the rate gradation properties of the motoneuron. The self-generated persistent inward current ('plateau current') is predominantly mediated by L-type Ca^{++} channels. Once started, such a current may sometimes even suffice to let a motoneuron continue firing repetitively, even if the synaptic excitation becomes interrupted ('plateau firing').

With regard to motoneurons, the earliest published examples of 'plateau-facilitating' post-synaptic

effects included monoaminergic actions in cat (noradrenalin, serotonin) and turtle (serotonin) spinal cord (for example, Hounsgaard et al., 1986). Since then, several other kinds of metabotropic receptors have been found whose activation may facilitate the emergence of plateau currents (Delgado-Lezama & Hounsgaard, 1999).

In addition to facilitating the emergence of plateau currents, motoneuron-modifying synapses can also cause a decrease in the size of the post-spike afterhyperpolarization (for example, Van Dongen et al., 1986; Hounsgaard & Kiehn, 1989), hence steepening the f-I relation of the motoneuron (for example, Hounsgaard & Kiehn, 1989). Thus, also in this manner synapses can change the motoneuronal responses to driving currents from elsewhere (for further references concerning these and other motoneuronal modifications, see Powers & Binder, 2001). Motoneurons innervating different kinds of muscle units are likely to differ in the characteristics of their plateau currents (Lee & Heckman, 1998). To what extent modifications of excitability and f-I relation take place in combination with the emergence of plateau currents is still unclear.

We do not yet understand much about the functional role of these various acute changes of motoneuronal activation properties. It is essential to be able to relate these properties to the manner in which motoneurons are used in motor behavior. Such problems are presently being tackled by several groups of investigators, typically using electromyographic techniques for the recording of motoneuronal discharges in awake animals and humans under different conditions (for example, rats, Eken, 1998; Gorassini et al., 1999; human subjects, Kiehn & Eken, 1997; Gorassini et al., 1998; Collins et al., 2002). The studies made so far give strong indications that motoneuronal plateau currents play a significant role in animal and human motor behavior under normal conditions, as well as, perhaps even more so, in

cases of long-term spasticity following damage to the central nervous system (Bennett et al., 2001). Possibly, plateau currents might contribute to the spontaneous motoneuronal activity often seen in patients after spinal cord injury (Zijdewind & Thomas, 2001).

In addition to the possible long-term effects on plateau-behavior in spasticity, various other kinds of chronic modifications of motoneurons are known, for example, changes in their activation and membrane properties following long-term alterations of motor activity, following changes of the innervation target, and so on (for further information and references, see Mendell et al., 1994; Munson et al., 1997; Wolpaw & Tennissen, 2001; Beaumont & Gardiner, 2002). Very little is known about the mechanisms and precise conditions underlying such long-term alterations; this field is important for further investigations.

CONCLUDING REMARKS: PROBLEMS AT THE OUTPUT?

In all motor behavior, the properties of the final common path of the motor system are important for defining how it should be run by neuron populations further upstream within the central nervous system. As I mentioned at the onset of this brief survey, a non-optimal function of such 'higher' mechanisms is probably responsible for most motor problems encountered by clumsy children. Are there any possibilities that the output system might, in itself, also be directly concerned in the production of 'clumsiness'?

I do not, of course, know the answer to this question. Nevertheless, I would like to mention at least one hypothetical risk factor for further consideration. The short-term modifications of how motoneurons respond to synaptic activation—for example, as influenced by monoaminergic or other metabotropic synapses—might, if badly integrated

into the total motor program, conceivably lead to unpredictable variations in the forces produced by sets of activated muscles, thereby contributing to a production of 'clumsiness'. Whether such (or other) problems at the output actually exist in clumsy children is a question for further experimental research.

REFERENCES

- Beaumont E, Gardiner P. 2002. Effects of daily spontaneous running on the electrophysiological properties of hindlimb motoneurons in rats. *J Physiol* 540: 129–138.
- Bennett DJ, Li Y, Harvey PJ, Gorassini M. 2001. Evidence for plateau potentials in tail motoneurons of awake chronic spinal rats with spasticity. *J Neurophysiol* 86: 1972–1982.
- Binder MD, Heckman CJ, Powers RK. 1996. The physiological control of motoneuron activity. In: Rowell LB, Shepherd JT, eds, *Handbook of Physiology. Section 12, Exercise: Regulation and Integration of Multiple Systems*. New York, NY, USA-Oxford, UK: Am Physiol Soc; 3–53.
- Binder-Macleod SA. 1992. Force-frequency relation in skeletal muscle. In: Currier, DP, Nelson, RM, eds, *Dynamics of Human Biological Tissues*. Philadelphia, Pennsylvania, USA: F.A. Davis; 97–113.
- Burke RE. 1981. Motor units: anatomy, physiology and functional organization. In: Brooks VB, ed, *Handbook of Physiology—The Nervous System, Sec. 1, Vol. II*. Bethesda, Maryland, USA; Am Physiol Soc; 345–422.
- Collins DF, Burke D, Gandevia SC. 2002. Sustained contractions produced by plateau-like behaviour in human motoneurons. *J Physiol* 538: 289–301.
- Delgado-Lezama R, Hounsgaard J. 1999. Adapting motoneurons for motor behavior. *Prog Brain Res* 123: 57–63.
- Eken T. 1998. Spontaneous electromyographic activity in adult rat soleus muscle. *J Neurophysiol* 80: 365–376.
- Emonet-Denand F, Laporte Y, Proske U. 1971. Contraction of muscle fibers in two adjacent muscles innervated by branches of the same motor axon. *J Neurophysiol* 34: 132–138.
- English AW, Letbetter WD. 1982. A histochemical analysis of identified compartments of cat lateral

- gastrocnemius muscle. *Anat Rec* 204: 123–130.
- Gorassini M, Bennett DJ, Kiehn O, Eken T, Hultborn H. 1999. Activation patterns of hindlimb motor units in the awake rat and their relation to motoneuron intrinsic properties. *J Neurophysiol* 82: 709–717.
- Gorassini MA, Bennett DJ, Yang JF. 1998. Self-sustained firing of human motor units. *Neurosci Lett* 247: 13–16.
- Granit R, Kernell D, Lamarre Y. 1966. Algebraical summation in synaptic activation of motoneurons firing within the 'primary range' to injected currents. *J Physiol* 187: 379–399.
- Heckman CJ, Lee RH. 1999. Synaptic integration in bistable motoneurons. *Prog Brain Res* 123: 49–56.
- Henneman E, Mendell LM. 1981. Functional organization of motoneuron pool and its inputs. In: Brooks VB, ed, *Handbook of Physiology—The Nervous System II, Part 1*. Bethesda, Maryland, USA: Am Physiol Soc; 423–507.
- Hensbergen E, Kernell D. 1992. Task-related differences in distribution of electromyographic activity within peroneus longus muscle of spontaneously moving cats. *Exp Brain Res* 89: 682–685.
- Hoffer JA, Loeb GE, Sugano N, Marks WB, O'Donovan MJ, Pratt CA. 1987. Cat hindlimb motoneurons during locomotion. III. Functional segregation in sartorius. *J Neurophysiol* 57: 554–562.
- Houngaard J, Hultborn H, Kiehn O. 1986. Transmitter-controlled properties of α -motoneurons causing long-lasting motor discharge to brief excitatory inputs. *Prog Brain Res* 64: 39–49.
- Houngaard J, Kiehn O. 1989. Serotonin-induced bistability of turtle motoneurons caused by a nifedipine-sensitive calcium plateau potential. *J Physiol* 414: 265–282.
- Hultborn H. 1999. Plateau potentials and their role in regulating motoneuronal firing. *Prog Brain Res* 123: 39–48.
- Kernell D. 1969. Synaptic conductance changes and the repetitive impulse discharge of spinal motoneurons. *Brain Res* 15: 291–294.
- Kernell D. 1992. Organized variability in the neuromuscular system: A survey of task-related adaptations. *Arch Ital Biol* 130: 19–66.
- Kernell D, Hultborn H. 1990. Synaptic effects on recruitment gain: a mechanism of importance for the input-output relations of motoneurons pools? *Brain Res* 507: 176–179.
- Kiehn O, Eken T. 1997. Prolonged firing in motor units: evidence of plateau potentials in human motoneurons? *J Neurophysiol* 78: 3061–3068.
- Lee RH, Heckman CJ. 1998. Bistability in spinal motoneurons in vivo: systematic variations in rhythmic firing patterns. *J Neurophysiol* 80: 572–582.
- Mendell LM, Collins WFI, Munson JB. 1994. Retrograde determination of motoneuron properties and their synaptic input. *J Neurobiol* 25: 707–721.
- Munson JB, Foehring RC, Mendell LM, Gordon T. 1997. Fast-to-slow conversion following chronic low-frequency activation of medial gastrocnemius muscle in cats. II. Motoneuron properties. *J Neurophysiol* 77: 2605–2615.
- Powers RK, Binder MD. 1995. Effective synaptic current and motoneuron firing rate modulation. *J Neurophysiol* 74: 793–801.
- Powers RK, Binder MD. 2000. Summation of effective synaptic currents and firing rate modulation in cat spinal motoneurons. *J Neurophysiol* 83: 483–500.
- Powers RK, Binder MD. 2001. Input-output functions of mammalian motoneurons. *Rev Physiol Biochem Pharmacol* 143: 137–263.
- Schwindt PC, Crill WE. 1980. Properties of a persistent inward current in normal and TEA-injected motoneurons. *J Neurophysiol* 43: 1700–1724.
- Sekiya H, Kojima Y, Hiramoto D, Mukuno K, Ishikawa S. 1992. Bilateral innervation of the musculus levator palpebrae superioris by single motoneurons in the monkey. *Neurosci Lett* 146: 10–12.
- ter Haar Romeny BM, Denier van der Gon JJ, Gielen CCAM. 1984. Relation between location of a motor unit in the human biceps brachii and its critical firing levels for different tasks. *Exp Neurol* 85: 631–650.
- Van Dongen PA, Grillner S, Hokfelt T. 1986. 5-Hydroxy tryptamine (serotonin) causes a reduction in the afterhyperpolarization following the action potential in lamprey motoneurons and premotor interneurons. *Brain Res* 366: 320–325.
- Wolpaw JR, Tennissen AM. 2001. Activity-dependent spinal cord plasticity in health and disease. *Annu Rev Neurosci* 24: 807–843.
- Zijdewind I, Thomas CK. 2001. Spontaneous motor unit behavior in human thenar muscles after spinal cord injury. *Muscle Nerve* 24: 952–962.