

Origin and Development of Muscle Cramps

Marco Alessandro Minetto¹, Aleš Holobar², Alberto Botter³, and Dario Farina⁴

¹Division of Endocrinology, Diabetology and Metabolism, Department of Internal Medicine, University of Turin, Turin, Italy; ²Faculty of Electrical Engineering and Computer Science, University of Maribor, Maribor, Slovenia;

³Laboratory for Engineering of the Neuromuscular System, Department of Electronics and Telecommunications, Politecnico di Torino, Turin, Italy; and ⁴Department of Neurorehabilitation Engineering, Bernstein Focus Neurotechnology Göttingen, Bernstein Center for Computational Neuroscience, University Medical Center Göttingen, Georg-August University, Göttingen, Germany.

MINETTO, M.A., A. HOLOBAR, A. BOTTER, and D. FARINA. Origin and development of muscle cramps. *Exerc. Sport Sci. Rev.*, Vol. 41, No. 1, pp. 3–10, 2013. *Cramps are sudden, involuntary, painful muscle contractions. Their pathophysiology remains poorly understood. One hypothesis is that cramps result from changes in motor neuron excitability (central origin). Another hypothesis is that they result from spontaneous discharges of the motor nerves (peripheral origin). The central origin hypothesis has been supported by recent experimental findings, whose implications for understanding cramp contractions are discussed.* **Key Words:** cramp discharge, cramp threshold frequency, electromyography, exercise-associated muscle cramps, motor unit action potentials, motor neurons

INTRODUCTION

A muscle cramp is a sudden, involuntary, painful contraction of a muscle or part of it, self-extinguishing within seconds to minutes and is often accompanied by a palpable knotting of the muscle. The cramp contractions are associated with repetitive firing of motor unit action potentials. This myoelectric activity has been referred to as “cramp discharge” (16).

Cramps may occur in patients with lower motor neuron disorders, neuropathies, metabolic disorders, and acute extracellular volume depletion. However, they also often occur in healthy subjects with no history of nervous or metabolic disorders, such as during sleep, pregnancy, and strenuous physical exercise. The latter cramps have been defined as “benign cramps” or “idiopathic cramps” or “cramps with no apparent cause” (16).

Muscle cramping during or immediately after physical exercise was first reported more than 100 yr ago in miners working in hot and humid conditions (28). Dehydration (and/or

electrolyte depletion) often is given as an explanation for muscle cramps occurring in workers and athletes, although this claim is not supported by scientific evidence (28–30). The main risk factors for exercise-associated muscle cramps include family history of cramping, previous occurrence of cramps during or after exercise, increased exercise intensity and duration, and inadequate conditioning for the activity (28–30).

Norris *et al.* (22) reported a high prevalence of benign cramps in a wide group of healthy young subjects enrolled in an exercise class; 115 (95%) of 121 had experienced spontaneous muscle cramps at least once. Jansen *et al.* (7) reported an overall yearly incidence of cramps in 37% of healthy adults. Similarly, the lifetime prevalence of cramps in athletes (marathon runners) and sedentary healthy subjects (aged 65 yr or older) has been reported to be as high as 30% to 50% (9,16,28).

A cramp can be distinguished from spasms (*i.e.*, any involuntary and abnormal muscle contraction, regardless of whether it is painful) or generic painful contractions based on clinical and electrophysiological criteria. For example, muscle contractures resemble cramps because they are involuntary and painful. However, they are electrically silent. Dystonias, such as cervical dystonia (spasmodic torticollis) or focal hand dystonia (so called musician’s or writer’s cramp), are different from cramps because they are involuntary sustained co-contractions of several muscles producing slow, twisting, and repetitive movements or abnormal postures that are not relieved by muscle stretching. Conversely, cramps present

Address for correspondence: Marco Alessandro Minetto, M.D., Ph.D., Division of Endocrinology, Diabetology and Metabolism, Department of Internal Medicine, University of Turin, Molinette Hospital, Corso Dogliotti 14, 10126 Torino, Italy (E-mail: marco.minetto@unito.it).

Accepted for publication: August 20, 2012.

Associate Editor: Roger M. Enoka, Ph.D.

0091-6331/4101/3–10
Exercise and Sport Sciences Reviews
Copyright © 2012 by the American College of Sports Medicine

unique clinical features: a) they are acutely painful (this may result in persistent soreness and increased levels of circulating muscle proteins); b) they present an involuntary explosive onset and gradual spontaneous resolution or sudden termination with muscle stretching; c) only one muscle or a part of it is involved; d) they are associated with both modest and forceful contractions, especially in shortened muscles (16); and e) they preferably occur in calf and foot muscles, followed by the hamstrings and the quadriceps.

The purpose of this review is to present recent experimental findings providing new insights into cramp pathophysiology and to discuss their implications for understanding cramp contractions in pathology and consequent to exercise.

LABORATORY METHODS FOR STUDYING MUSCLE CRAMPS

Cramp pathophysiology has been poorly understood partly because of the unpredictable occurrence of cramps that makes them relatively difficult to be studied in classic experimental settings. Some physiological experimental procedures have been used to induce cramps in healthy subjects. Examples of these procedures are maximal contractions, applied in the triceps surae (10,22,24–26), flexor hallucis brevis (3), biceps brachii (22), and quadriceps femoris (22), or a series of calf-fatiguing exercises (8). Cramps in the triceps surae also have been experimentally elicited by stimulating the calf Ia afferents with Achilles tendon taps/vibration (1,2) and by nociceptive stimulation of myofascial trigger points (6). Furthermore, cramps of the flexor hallucis brevis have been elicited by repetitive magnetic stimulation of the posterior tibial nerve (4).

Among the methods for eliciting cramps, electrical stimulation has been used often in both healthy subjects and patients. This method has been applied at intensities below the motor threshold to induce cramps in the triceps surae (1,2), quadriceps femoris, or upper limb muscles (2) or at supra-maximal intensities in upper limb muscles (23) and in the flexor hallucis brevis (3,11,13–15,27). In these experiments, the minimum frequency of the electrical stimulation burst capable of inducing a cramp has been termed the “threshold frequency.” It has been observed that the threshold frequency for cramp induction is lower in cramp-prone subjects compared with subjects with no history of cramps (3,14,17,19). For example, Miller and Knight (14) found a threshold frequency for the flexor hallucis brevis muscle of approximately 15 Hz in subjects with a history of cramping and of approximately 25 Hz in individuals not prone to cramping.

In addition to stimulating over the nerves, electrical stimulation over the muscle motor point (which stimulates the nerve terminal branches) also has been used to induce cramps. We have adopted this method, which has some advantages over nerve stimulation (19), for cramp induction in several muscles of the lower limb, such as the abductor hallucis (17–21), flexor hallucis brevis (17), and gastrocnemii (17). Figure 1 shows examples of electromyographic (EMG) activity of “experimental cramps” elicited with this method in four muscles of a representative healthy subject. From these recordings, it is worth noting that an involuntary EMG activity is present in the cramping muscle, whereas only fasciculation

potentials are observed in synergistic muscles. Conversely, these four muscles (the two gastrocnemii and two intrinsic foot muscles) work in synergy during a voluntary contraction.

The experimental elicitation of cramps by stimulation methods provided some general observations on the nature of cramps. First, the critical factor for cramp induction is the frequency of the stimulation burst (3,11,13,14,18,19,27) that thus can be used as a measure of the susceptibility to cramps. Second, some muscles are more susceptible to electrically elicited cramps than others, independent of the side dominance (17). For example, we found that leg muscles are more resistant to cramp induction than foot muscles (17). Third, cramps cannot be elicited if the muscle does not shorten during the stimulation (3). The factors and mechanisms underlying the differences in cramp susceptibility between different muscles and subjects still are not understood fully.

CENTRAL OR PERIPHERAL ORIGIN?

Although it is generally accepted that cramps have a neurogenic nature, their origin has been long discussed (12,16). One hypothesis is that cramps result from the hyperexcitability of motor neurons (central or spinal origin hypothesis). Another hypothesis is that cramps result from spontaneous discharges of the motor nerves or abnormal excitation of the terminal branches of motor axons (peripheral or axonal origin hypothesis).

On one hand, the mechanism that could underlie motor neuron hyperexcitability is the development of persistent inward currents in spinal motor neurons after contraction- or stimulation-mediated activation of sensory afferents (1,2,20,21,26). Generation of persistent inward currents modifies the relation between synaptic input and motor neuron output, so that afferent inputs converging on the motor neurons during cramp development are amplified and prolonged.

On the other hand, spontaneous discharges of the motor nerves or abnormal excitation of the terminal branches of motor axons may be induced by mechanical action on the nerve terminals and changes in volume or electrolyte concentration of the extracellular fluid (as in dehydration and hemodialysis) around the epineurium and end plates during muscle shortening (3,24). This, in turn, could imply the generation of ectopic axonal discharges (such as fasciculation potentials) that then spread to neighboring excitable axons by direct contact (cross excitation or ephaptic activation) and eventually produce the cramp discharge.

The peripheral origin and central origin of cramps have been discussed and supported in several studies. The Table lists the experimental observations providing support for each hypothesis. It is worth mentioning that some experimental findings (e.g., cramp inhibition by muscle stretching, cramp spreading, facilitation of cramp induction in the shortened muscle) could be explained by both hypotheses.

MOTOR UNIT ACTIVITY DURING MUSCLE CRAMPS

Relevant information into the mechanism of cramp generation has been provided by selective intramuscular

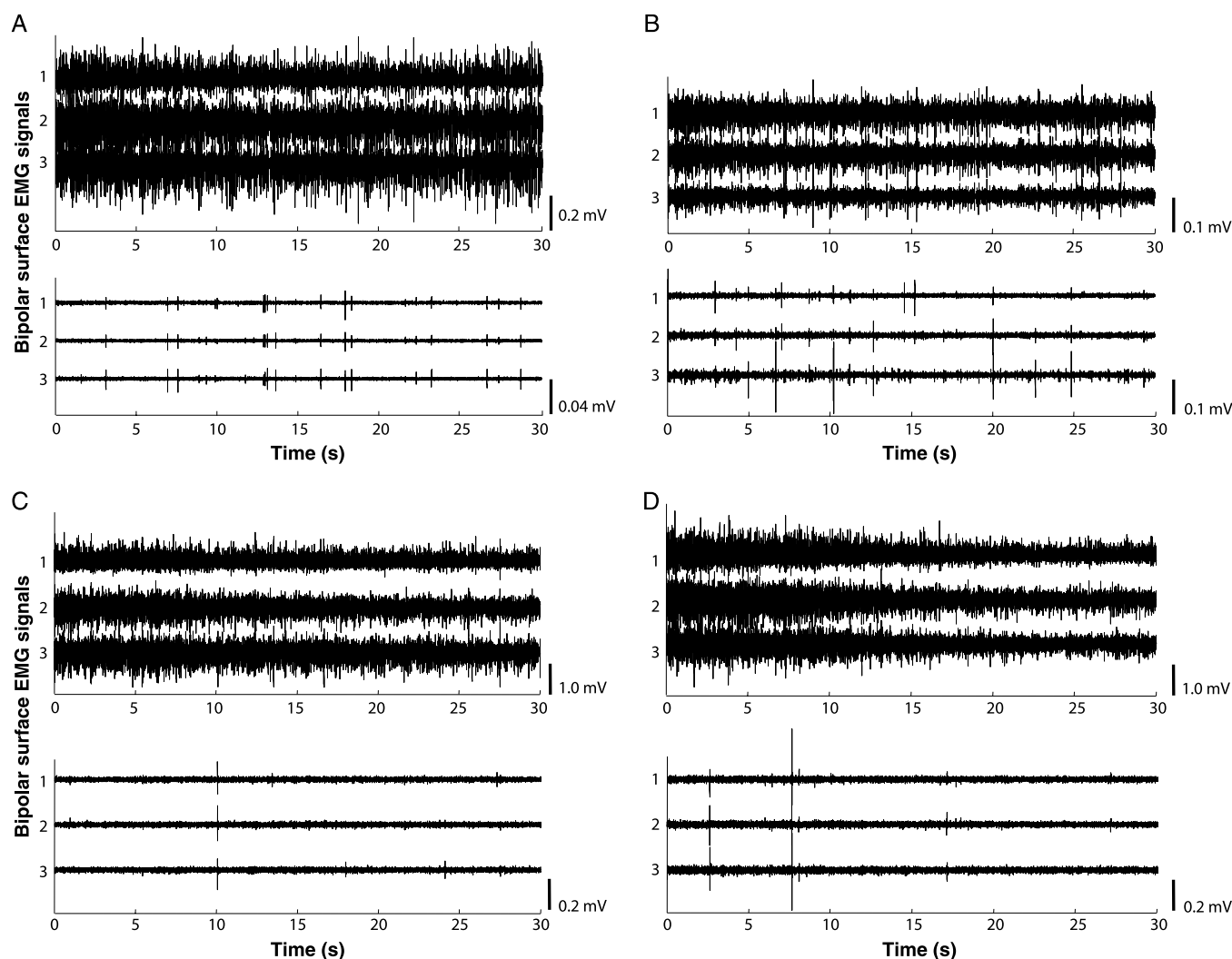


Figure 1. Surface electromyography (EMG) during cramps elicited in the abductor hallucis (A) and in the flexor hallucis brevis (B) of a representative subject (by electrical stimulation of the respective muscle motor points). Time 0 indicates the end of the stimulation. In both panels, three bipolar surface EMG signals are shown for both the cramping muscle (upper signals) and the synergistic muscle. In both panels, only fasciculation potentials are evident in the surface EMG recordings of the synergistic muscle (lower signals), without concurrent activation of the two muscles. Surface EMG during cramps elicited in the lateral (C) and medial gastrocnemius (D) of the same subject as in (A) and (B). [Adapted from (17). Copyright © 2009 John Wiley and Sons. Used with permission.]

recordings of muscle electrical activity during cramps. One of the main observations has been that action potentials of similar shape repeat consistently over time during cramps, so that they are presumably motor unit action potentials (20–22,26). Moreover, we (20) and others (26) found that the discharge rates of these action potentials are comparable to those observed during voluntary contractions, although the interspike interval variability is greater. We also observed that the discharge rates of different motor units during cramp are partly correlated (20), showing common oscillations (although with larger delays with respect to those observed during voluntary contractions) that could be related to similar afferent synaptic input (but delayed in time) that projects to different motor neurons. Moreover, motor unit discharge rates decrease over time during cramp development (20,21,26), which is consistent with the decrease in motor unit discharge rate during sustained voluntary contractions. Furthermore, when a motor unit stops discharging during a cramp, the minimal discharge rate that it reaches is in the range of 4 to 8 pps

(20,21), which corresponds to the minimal rate at which motor neurons discharge action potentials in voluntary contractions.

These observations suggest that the action potentials observed during cramps are generated at the motor neuron soma and that afferent synaptic inputs to the motor neurons influence cramp development and extinction. However, such observations do not exclude the possibility that cramps can be elicited exclusively at the periphery and that cramps elicited by only peripheral mechanisms may be similar to ordinary cramps. The study of contractions induced after peripheral nerve block has more recently elicited the relative peripheral and central role in the cramp origin and development.

CONTRACTIONS ELICITED WITH NERVE BLOCKS

Recent findings have proved unambiguously the relevance of central mechanisms in the generation and development of muscle cramps, as they are observed in normal conditions

TABLE. Experimental findings supporting the central and peripheral hypothesis of cramp origin.

Experimental Model of Cramp Induction	Muscle(s) Studied	Results and Overall Conclusion	Study
In Support of the Central Origin Hypothesis			
Electrical stimulation of the nerve trunk	Upper limb muscles (first interosseus, abductor digiti minimi, flexor carpi ulnaris)	No induction of cramps after anesthetic block of the ulnar nerve, despite high frequency stimulation at the wrist	Obi <i>et al.</i> (23)
Electrical stimulation of the muscle motor point	Abductor hallucis	No electrical induction of a second cramp a few minutes after a first cramp as a possible result of either sensory axon hyperpolarization and reduced axonal excitability or reduced motor neuron excitability induced by the first cramp	Minetto <i>et al.</i> (20)
Maximal voluntary contraction	Triceps surae	Depression of tonic vibration reflex after the end of a cramp of the homologous muscle as a result of cramp-induced increase in presynaptic inhibition of sensory afferents	Ross and Thomas (26)
Prolonged (60–90 s) voluntary contraction	Triceps surae	H-reflex enhancement after the end of a cramp of the homologous muscle, with no H-reflex change for the contralateral muscle, as a result of cramp-induced increase in the excitability of the motor neuron pool	Ross (25)
Electrical stimulation of the nerve trunk, tendon tapping, tendon vibration	Triceps surae, quadriceps, flexor carpi radialis, flexor digitorum, adductor pollicis	Cramp induction through stimulation of sensory afferents	Baldissera <i>et al.</i> (1,2)
Nociceptive stimulation of myofascial trigger points	Triceps surae	Cramp induction by nociceptive activation	Ge <i>et al.</i> (6)
Electrical stimulation of the nerve trunk	Flexor hallucis brevis	Facilitation of electrical induction of cramps by nociceptive stimulation of sensory afferents	Serrao <i>et al.</i> (27)
Anecdotal observation		Facilitation of cramp induction in shortened muscle, which could imply relaxation of tendon insertions and decrease of inhibitory afferent inputs from Golgi tendon organs	Jansen <i>et al.</i> (7)
Maximal voluntary contraction	Rectus femoris, triceps surae	Cramp inhibition by muscle stretching as a result of activation of the disynaptic inhibitory pathway from Golgi tendon organs	Norris <i>et al.</i> (22); Ross and Thomas (26)
Electrical stimulation of the nerve trunk, tendon tapping, tendon vibration	Triceps surae, adductor pollicis	Cramp inhibition by electrical stimulation of cutaneous afferents	Baldissera <i>et al.</i> (2)
Maximal voluntary contraction	Triceps surae	Cramp inhibition by electrical stimulation of tendon afferents	Khan and Burne (10)
Electrical stimulation of the nerve trunk	Triceps surae	Cramp inhibition by a single maximal electrical stimulus to the motor axons producing antidromic invasion and/or Renshaw inhibition of the motor neurons	Baldissera <i>et al.</i> (1,2)
Electrical stimulation of the nerve trunk	Flexor hallucis brevis	Cramp inhibition by pickle juice ingestion, as a possible result of an inhibitory oropharyngeal reflex that reduces motor neuron activity to the cramping muscle	Miller <i>et al.</i> (15)
Electrical stimulation of the muscle motor point	Abductor hallucis, flexor hallucis brevis, triceps surae	Presence of fasciculations of the synergistic muscles, as a result of cramp-induced increase in the excitability of synergistic motor neuron pools	Minetto and Botter (17)
Electrical stimulation of the muscle motor point	Abductor hallucis	Cramp spreading over a large muscle area, as a result of spreading of afferent input over time to the motor neuron population	Minetto <i>et al.</i> (20)
Maximal voluntary contraction	Rectus femoris	Modulation of cramp intensity by voluntary contraction of the contralateral synergistic muscle (cramp intensity increase) and of the ipsilateral antagonist muscle (cramp intensity decrease)	Norris <i>et al.</i> (22)
Electrical stimulation of the nerve trunk	Upper limb muscles	Effectiveness of drugs acting on the central nervous system (diazepam, baclofen) in reducing the cramp susceptibility	Obi <i>et al.</i> (23)
Electrical stimulation of the nerve trunk, electrical stimulation of the muscle motor point, maximal voluntary contraction	Abductor hallucis; triceps surae; rectus femoris	Properties of action potentials detected during cramps resemble motor unit action potentials detected during voluntary contractions	Minetto <i>et al.</i> (20,21); Norris <i>et al.</i> (22); Ross and Thomas (26)

TABLE. (Continued)

Experimental Model of Cramp Induction	Muscle(s) Studied	Results and Overall Conclusion	Study
In Support of the Peripheral Origin Hypothesis			
Electrical stimulation of the nerve trunk	Flexor hallucis brevis	Cramp induction by electrical stimulation distal to a peripheral nerve block	Bertolasi <i>et al.</i> (3); Lambert (11)
Electrical stimulation of the nerve trunk	Flexor hallucis brevis	Facilitation of cramp induction in shortened muscle, which could imply reduction of extracellular space and increased concentration of ions mediating ectopic ephaptic activation of motor axons	Bertolasi <i>et al.</i> (3)
Electrical stimulation of the nerve trunk	Flexor hallucis brevis	Cramp inhibition by muscle stretching in presence of peripheral nerve block, as a possible result of interruption of the mechanical distortion of nerve terminals	Bertolasi <i>et al.</i> (3)
Anecdotal observation		Association between cramps and fasciculations (arising from the terminal portion of the motor axons) that frequently occur before and after cramps	Denny-Brown and Foley (5)
Maximal voluntary contraction	Triceps surae	Cramp spreading over a large muscle area, as a result of activation of adjacent motor nerve terminals by ephaptic transmission	Roeleveld <i>et al.</i> (24)

(21). We electrically elicited muscle contractions in the abductor hallucis of healthy subjects in the presence (blocked condition) and absence (intact condition) of a peripheral nerve block (21). Figure 2 shows examples of EMG activity during such contractions. In these examples, the duration (55–75 s) and intensity of the contractions elicited in the intact condition were substantially greater than the duration (1.5–5 s) and intensity of those elicited in the blocked condition. In addition, the stimulation threshold frequencies for inducing these contractions were greater for the blocked (16 Hz in the three subjects) compared with those for the intact condition (10 Hz in two subjects and 12 Hz in one subject). The motor unit activity detected during the intact condition presented the typical characteristics of the motor neuron discharges, including range of discharge rates and decline in discharge rates over time, whereas the motor unit activity in the blocked condition presented the characteristics of the spontaneous discharge of motor nerves, including short interval of activity, high discharge rates, and high discharge variability (Fig. 3).

As for the representative examples shown in Figure 2, we found that cramp intensity and duration were greater in the intact condition with respect to the blocked condition in a larger experimental group of subjects (21). As for the representative examples shown in Figure 3, we found that motor unit discharge behavior showed distinct patterns between the two experimental conditions; the short-lasting muscle activity generated by peripheral stimulation in the blocked condition did not resemble the cramp discharge and was probably not the triggering mechanism underlying cramp generation because it was generated at greater threshold. Previous studies indicated in the periphery the generation of ordinary cramps because some contractions could be induced by electrical stimulation distal to a peripheral nerve block (3,11). However, such studies did not compare the peripherally elicited “cramps” with cramps elicited with the intact spinal loop. By doing so, it would have been clear that the small contractions arising with peripheral nerve block are of a very different nature than the ordinary cramps (21). One of the main differences is that the cramp threshold frequency is substantially lower when the spinal loop is intact. Because cramp threshold frequency is related to the individual

susceptibility to cramping (3,14,17,19), the cramp threshold differences between the intact and blocked condition may be interpreted as indirect evidence that cramp elicitation is triggered by the afferent inputs received by the motor neurons. The afferent pathways that influence the cramp threshold (inputs from muscle spindles, muscle mechanoreceptors and metaboreceptors, tendon afferents, cutaneous afferents) may be the same reflex circuitries that are active in sustaining the cramp. In agreement with these observations, a plausible model of cramp induction and development that involves spinal pathways consists of a positive feedback loop, in which motor neurons receive afferent inputs, resulting in hyperexcitability. It is presently unknown whether the positive feedback loop is triggered by neural changes that occur at the receptor level or at the spinal interneuron level and what is the exact mechanism underlying the receptor or spinal network changes in excitability.

PATHOPHYSIOLOGICAL AND CLINICAL IMPLICATIONS

Despite their “benign” nature, cramps are often very uncomfortable. Moreover, exercise-associated muscle cramps may significantly impair athletic performance.

Schweltnus (28–30) was the first who proposed an “altered neuromuscular control hypothesis” for the etiology of exercise-associated muscle cramps. This hypothesis was based first on the observation that the susceptibility to cramping increases after fatiguing exercise. Sustained muscle contraction, for example, resulted in biceps brachii cramps in 18% of 115 healthy subjects before 20 to 30 min of fatiguing exercise and in 26% afterward (22). Second, the development of exercise-associated muscle cramps is more common in the latter stages of a race (*i.e.*, after the development of muscle fatigue), and the onset of both fatigue and cramps can be delayed by carbohydrate-electrolyte supplementation during fatiguing exercise (8). Based on these considerations, Schweltnus (28–30) suggested that an altered neuromuscular control during fatigue (increased excitatory and decreased inhibitory

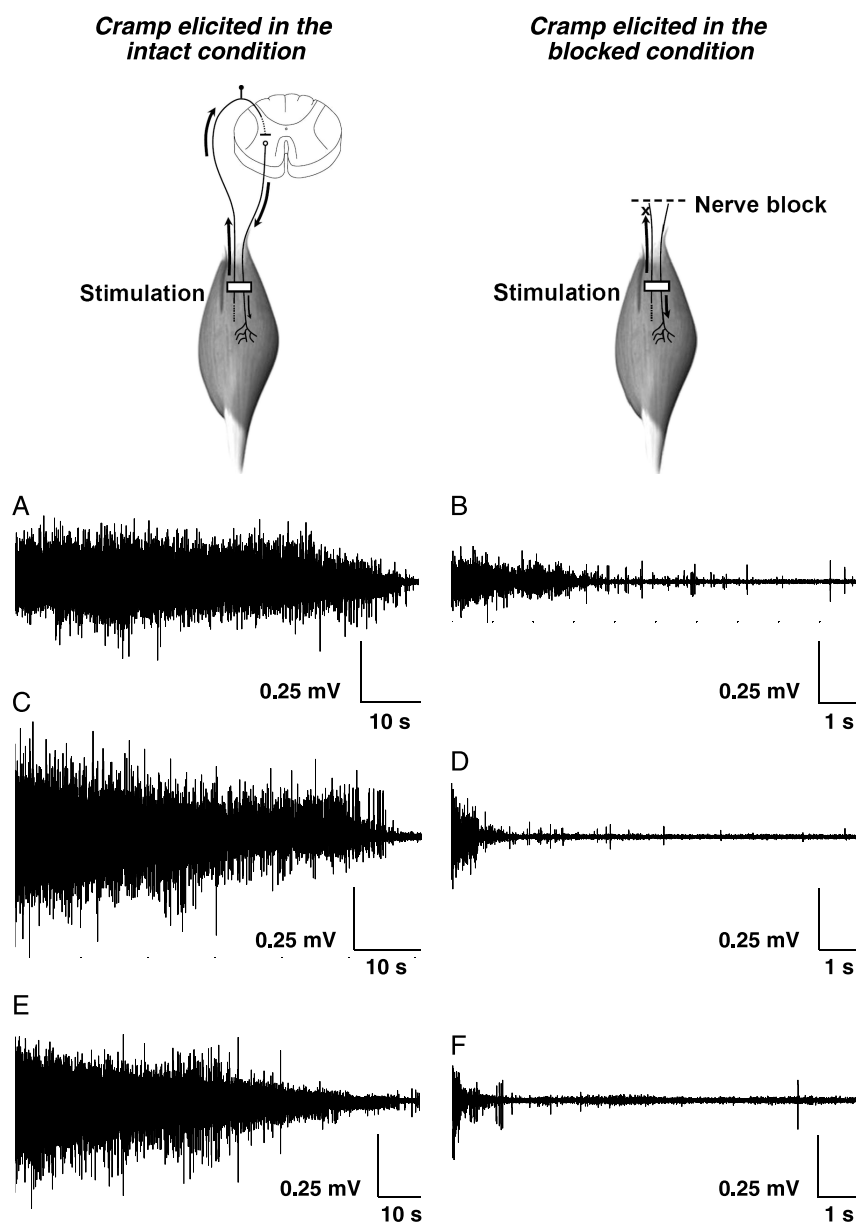


Figure 2. Surface electromyography (EMG) during cramps elicited in the intact condition ((A), (C), (E)) and nerve-blocked condition ((B), (D), (F)) in three subjects (starting from the end of the stimulation burst). Note different horizontal scales. [Adapted from (21). Copyright © 2011 John Wiley and Sons. Used with permission.]

afferent inputs to motor neurons, resulting in sustained motor neuron activity) could underlie the origin of exercise-associated muscle cramps.

Schweltnus' hypothesis is in agreement with the role of spinal pathways in the cramp origin and development, which has been observed in laboratory conditions. Fatigue- or contraction- or stimulation-induced changes in afferent synaptic input to motor neurons may change the excitability of motor neurons, thus producing the cramp discharge that can be, in turn, amplified by increased supraspinal motor drive and/or increased neuromodulatory inputs to motor neurons. Motor neuron hyperexcitability resulting from afferent synaptic inputs (and amplified by supraspinal inputs) is the plausible common mechanism underlying different types of

cramp contractions, such as cramps occurring during maximal nonfatiguing contraction, fatiguing exercise-associated cramps, cramps in patients undergoing hemodialysis, and cramps occurring in neurological and metabolic diseases associated with motor neuron hyperexcitability. Future studies directed to the investigation of motor neuron excitability during cramps in humans and to the analysis of cortical excitability by magnetic stimulation applied to the motor cortex would shed light into the central (spinal and cortical) contributions to the different types of cramp contractions. This model of cramp induction is in agreement with the effectiveness of drugs acting on the central nervous system (baclofen, diazepam, gabapentin, carbamazepine) in reducing cramp frequency or susceptibility (23). On this note, it is

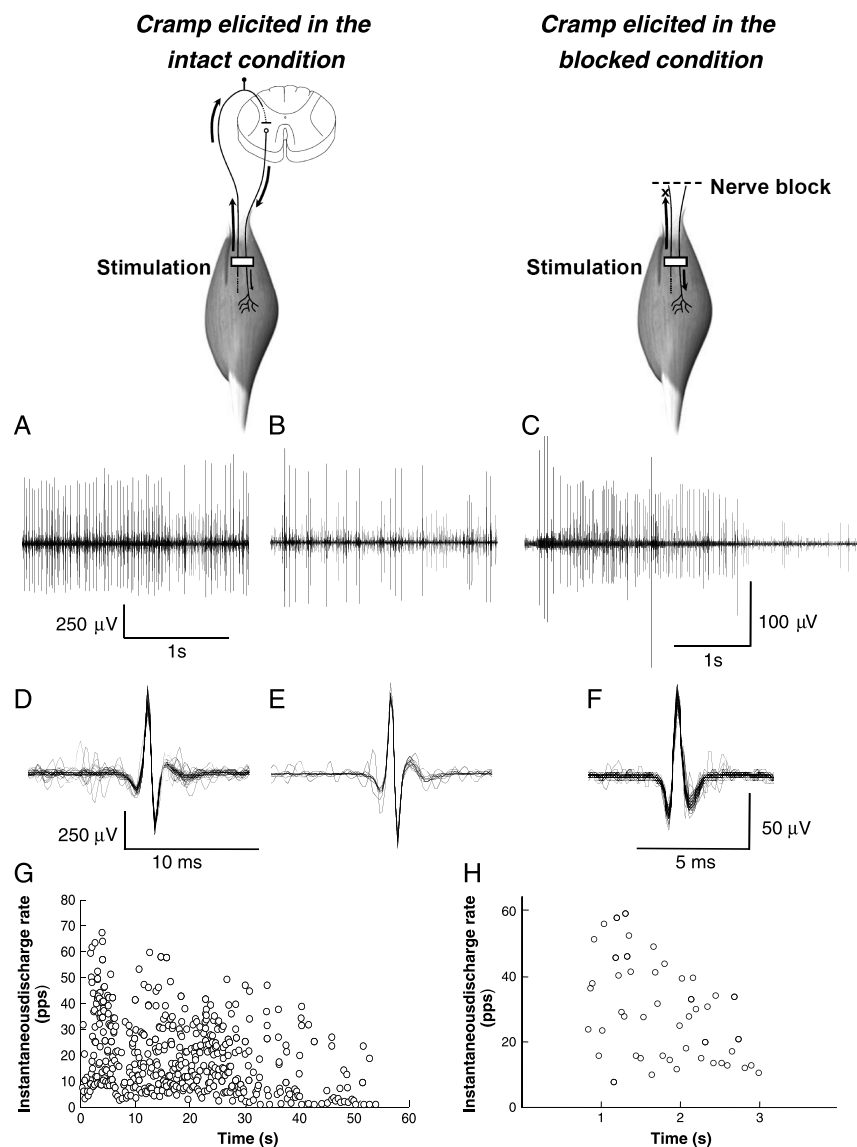


Figure 3. Intramuscular electromyographic (EMG) signals during the first (A) and last (B) 2 s of activation of a motor unit detected during a cramp elicited in the intact condition in one subject. D. and E. The action potentials detected during the intact condition for the first and last 2 s of contraction. The similarity in shape and amplitude of the action potentials indicates that they were most likely generated by the same unit. C. Intramuscular EMG signals during a cramp elicited in the nerve-blocked condition in the same subject as in (A) and (B). F. The action potentials detected during the nerve-blocked condition. G. Instantaneous discharge rates of the motor unit identified in the intact condition (from the intramuscular signals shown in (A) and (B)) for the entire duration of its activation interval. H. Instantaneous discharge rates of the motor unit identified in the nerve-blocked condition (from the intramuscular signal shown in (C)) for the entire duration of its activation interval. [Adapted from (21). Copyright © 2011 John Wiley and Sons. Used with permission.].

worth mentioning that centrally acting drugs are used frequently in clinical practice for the management and treatment of cramps (9,16,23), although few clinical trials assessed their efficacy for this indication.

CONCLUSIONS

Recent experimental findings have proved unambiguously the relevance of spinal mechanisms in the generation and development of muscle cramps. These findings are important for identifying the most effective and safe medications for managing (preventing or reducing the occurrence of) cramps. However,

several unresolved issues in cramp pathophysiology and management still remain and require further investigation. For example, the factors underlying the intermuscle and intersubject variability in cramp propensity are still unclear, as well as the reasons for the generation of pain during cramps.

Acknowledgments

The authors are grateful to Prof. Martin McDonagh (University of Birmingham, Birmingham, UK) for useful discussions and for commenting on a preliminary version of this article.

The authors' work related to this review was supported by the bank foundation "Compagnia di San Paolo" (Project "Neuromuscular Investigation and

Conditioning in Endocrine Myopathy") (M.A.M.); a Marie Curie reintegration grant within the European Community Framework Programme (iMOVE, Contract No. 239216) (A.H.); the ERC Advanced Research Grant DEMOVE ("Decoding the Neural Code of Human Movements for a New Generation of Man-machine Interfaces"; no. 267888) (D.F.).

None of the authors have received or will receive benefits for personal or professional use from companies or manufacturers who will benefit from the results of the present study. No funding was received for this work from any of the following organizations: National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute.

References

- Baldissera F, Cavallari P, Dworzak F. Cramps: a sign of motoneurone "bistability" in a human patient. *Neurosci. Lett.* 1991; 133:303–6.
- Baldissera F, Cavallari P, Dworzak F. Motor neuron "bistability." A pathogenetic mechanism for cramps and myokymia. *Brain.* 1994; 117(Pt 5): 929–39.
- Bertolasi L, De Grandis D, Bongiovanni LG, Zanette GP, Gasperini M. The influence of muscular lengthening on cramps. *Ann. Neurol.* 1993; 33:176–80.
- Caress JB, Bastings EP, Hammond GL, Walker FO. A novel method of inducing muscle cramps using repetitive magnetic stimulation. *Muscle Nerve.* 2000; 23:126–8.
- Denny-Brown D, Foley JM. Myokymia and the benign fasciculation of muscular cramps. *Trans. Assoc. Am. Phys.* 1948; 61:88–96.
- Ge HY, Zhang Y, Boudreau S, Yue SW, Arendt-Nielsen L. Induction of muscle cramps by nociceptive stimulation of latent myofascial trigger points. *Exp. Brain. Res.* 2008; 187:623–9.
- Jansen PH, Joosten EM, Vingerhoets HM. Muscle cramp: main theories as to etiology. *Eur. Arch. Psychiatry Neurol. Sci.* 1990; 239:337–42.
- Jung AP, Bishop PA, Al-Nawwas A, Dale RB. Influence of hydration and electrolyte supplementation on incidence and time to onset of exercise-associated muscle cramps. *J. Athl. Train.* 2005; 40:71–5.
- Katzberg HD, Khan AH, So YT. Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology.* 2010; 74:691–6.
- Khan SI, Burne JA. Reflex inhibition of normal cramp following electrical stimulation of the muscle tendon. *J. Neurophysiol.* 2007; 98:1102–7.
- Lambert E. Electromyography in amyotrophic lateral sclerosis. In: Norris FH, Kurland LT, editors. *Motor Neuron Disease: Research on Amyotrophic Lateral Sclerosis and Related Disorders.* New York: Grune and Stratton; 1968, p. 135–53.
- Layzer RB. The origin of muscle fasciculations and cramps. *Muscle Nerve.* 1994; 17:1243–9.
- Miller KC, Knight KL. Pain and soreness associated with a percutaneous electrical stimulation muscle cramping protocol. *Muscle Nerve.* 2007; 36:711–4.
- Miller KC, Knight KL. Electrical stimulation cramp threshold frequency correlates well with the occurrence of skeletal muscle cramps. *Muscle Nerve.* 2009; 39:364–8.
- Miller KC, Mack GW, Knight KL, et al. Reflex inhibition of electrically induced muscle cramps in hypohydrated humans. *Med. Sci. Sports Exerc.* 2010; 42:953–61.
- Miller TM, Layzer RB. Muscle cramps. *Muscle Nerve.* 2005; 32:431–42.
- Minetto MA, Botter A. Elicitability of muscle cramps in different leg and foot muscles. *Muscle Nerve.* 2009; 40:535–44.
- Minetto MA, Botter A, De Grandis D, Merletti R. Time and frequency domain analysis of surface myoelectric signals during electrically-elicited cramps. *Neurophysiol. Clin.* 2009; 39:15–25.
- Minetto MA, Botter A, Ravenni R, Merletti R, De Grandis D. Reliability of a novel neurostimulation method to study involuntary muscle phenomena. *Muscle Nerve.* 2008; 37:90–100.
- Minetto MA, Holobar A, Botter A, Farina D. Discharge properties of motor units of the abductor hallucis muscle during cramp contractions. *J. Neurophysiol.* 2009; 102:1890–901.
- Minetto MA, Holobar A, Botter A, Ravenni R, Farina D. Mechanisms of cramp contractions: peripheral or central generation? *J. Physiol.* 2011; 589(Pt 23):5759–73.
- Norris FH Jr, Gasteiger EL, Chatfield PO. An electromyographic study of induced and spontaneous muscle cramps. *Electroencephalogr. Clin. Neurophysiol.* 1957; 9:139–47.
- Obi T, Mizoguchi K, Matsuoka H, Takatsu M, Nishimura Y. Muscle cramp as the result of impaired GABA function—an electrophysiological and pharmacological observation. *Muscle Nerve.* 1993; 16:1228–31.
- Roeleveld K, van Engelen BG, Stegeman DF. Possible mechanisms of muscle cramp from temporal and spatial surface EMG characteristics. *J. Appl. Physiol.* 2000; 88:1698–706.
- Ross BH. *Muscle Cramp and the Hoffman Reflex.* XXth World Congress in Sports Medicine Handbook. Melbourne, Australia; 1974, p. 67–70.
- Ross BH, Thomas CK. Human motor unit activity during induced muscle cramp. *Brain.* 1995; 118(Pt 4):983–93.
- Serrao M, Arendt-Nielsen L, Ge HY, Pierelli F, Sandrini G, Farina D. Experimental muscle pain decreases the frequency threshold of electrically elicited muscle cramps. *Exp. Brain Res.* 2007; 182:301–8.
- Schwellnus MP. Muscle cramping in the marathon: aetiology and risk factors. *Sports Med.* 2007; 37:364–7.
- Schwellnus MP. Cause of exercise associated muscle cramps (EAMC)—altered neuromuscular control, dehydration or electrolyte depletion? *Br. J. Sports Med.* 2009; 43:401–8.
- Schwellnus MP, Derman EW, Noakes TD. Aetiology of skeletal muscle "cramps" during exercise: a novel hypothesis. *J. Sports Sci.* 1997; 15: 277–85.