REVIEW ARTICLE

Muscular cramp: causes and management

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Muscular cramp is a common symptom in healthy people, especially among the elderly and in young people after vigorous or peak exercise. It is prominent in a number of benign neurological syndromes. It is a particular feature of chronic neurogenic disorders, especially amyotrophic lateral sclerosis. A literature review was undertaken to understand the diverse clinical associations of cramp and its neurophysiological basis, taking into account recent developments in membrane physiology and modulation of motor neuronal excitability. Many aspects of cramping remain incompletely understood and require further study. Current treatment options are correspondingly limited.

Introduction

Muscle cramp is frequent in young people during vigorous exercise [1] and in older persons, especially in bed, when it mainly involves calf, foot and thigh muscles [2]. Some people are particularly susceptible to cramps during exercise. In an epidemiological survey among a healthy population in the Netherlands, the incidence of muscle cramp in the previous year was 37% [3]. Cramp is more frequent in certain disorders (Table 1), especially in neurogenic disorders [4] such as in peripheral neuropathies and amyotrophic lateral sclerosis (ALS) [5–7].

Exercise-associated muscular cramp (EAMC)

Exercise-associated muscular cramp may develop in single muscles, e.g. triceps surae, hamstrings or quadriceps, or as a more generalized phenomenon in multiple, sometimes symmetrical, lower limb muscles [1]. Dehydration and electrolyte disturbances have long been suspected as causing EAMC [8,9]. However, intensive research has not verified this hypothesis [10,11] and it is more likely that susceptibility to EAMC has a neurogenic basis. Subjects who frequently develop EAMC show lower cramp thresholds

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Table 1 Clinical associations with cramp

Exercise-induced cramp (mainly leg muscles)
Environmental cold, or contact with cold bedclothes
Dehydration, and heat cramp (salt deprivation)
Muscle hypoxia/ischaemia (vascular disease)
Drug-induced cramps (Table 3)
Pregnancy
Renal disease
Thyroid disease, especially hypothyroidism
Hypokalaemia, hypomagnesaemia, hypocalcaemia (parathyroid disease)
Restless legs syndrome
Varicose leg veins
Neurological disorders: amyotrophic lateral sclerosis, multiple sclerosis, peripheral neuropathies, cramp-fasciculation syndrome
Metabolic myopathies (electrically silent muscle contraction)
Toxins and poisons (snake and spider bites; strychnine)

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when cramps are elicited electrically [12] and, in the context of physical exertion, cramp vulnerability has been related to 'altered neuromuscular control'. Susceptibility to cramp is increased for as long as 60 min after fatiguing or peak exercise [13], e.g. toward the end of a soccer match. Although exercise-related cramp is often believed to be delayed by carbohydrate–electrolyte supplementation during the period of exercise [14], there is meagre supportive evidence for this concept. Increased excitatory and decreased inhibitory input to motor neurons during exercise, leading to sustained motoneuronal activity, enhanced by supraspinal projections to motoneurons, may induce cramp in the most exercised muscles [10,12]. This mechanism might account not only for exercise-related cramp but also for cramp associated with increased motoneuronal excitability in certain metabolic disorders, e.g. hypothyroidism and pregnancy, in haemodialysis and in ALS, and the post poliomyelitis syndrome. Cramp-alleviating therapies with actions on motor neuronal excitability, such as baclofen, diazepam and carbamazepine, would thus be expected to be effective [15].

This neurogenic hypothesis implies an abnormally enhanced response of intrinsic spinal cord circuitry to exercise-induced stimulation of mechanoceptors and nociceptors [16–18]. Indeed, incidental peripheral limb lesions causing pain (nociceptor activation), in particular arthritis or varicosities, are associated with an increased risk of muscular cramps [19,20]. Ge *et al*. [21] found that nociceptive stimulation of latent myofascial trigger points provoked cramps in more than 90% of tested subjects but non-painful stimulation of the same myofascial points did not. Painful injection of hypertonic saline into muscle also increased cramp susceptibility [22]. Thus, the threshold for cramp is reduced by nociceptive sensory input.

Clinical features of cramp

Cramp is a 'painful, spasmodic, involuntary, hard contraction of skeletal muscle' occurring during or immediately after exercise, in response to shortening of a muscle or to cold cutaneous stimulus, and relieved by stretching or massage [1,4]. Muscle cramps are typically of rapid or abrupt onset, often occurring during isometric contraction of a muscle that is already near-fully shortened. Cramps are frequently initiated in the context of minor muscle contraction, especially in a passive posture of near-maximal muscle shortening, e.g. in triceps surae. Contact between the lower leg and cold materials, e.g. bedsheets, is often noted as provoking cramps [2]. Environmental cold is probably also a precipitating factor in exercising athletes [23] although in this situation other exercise-related factors may be important. Heat cramps occur during exertion in hot, humid conditions.

Relief from the painful contraction of a cramped muscle can be expedited by forced passive stretch of the affected muscle, 'unlocking the cramp', when it usually becomes evident that only part of the muscle was contracted in the cramp [24]. Relief during muscle stretch is not instantaneous but develops over several seconds. If no active relief measures are undertaken the muscle will spontaneously gradually relax, but perhaps only after several minutes. For some hours, or even days, afterward the cramped portion of muscle tissue may be tender and painful, especially during voluntary contraction, suggesting that the degree of contraction during cramp was excessive and had caused local injury to muscle tissue or hypoxic/metabolic damage [4]. Since maximal physiological muscle contraction is not subsequently locally painful this post-cramp pain needs explanation – it cannot be related simply to physiological muscle contraction.

Neurophysiology of cramp

In idiopathic cramp and in cramp associated with chronic partial denervation motor units fire at unusually rapid rates – 50 Hz, or perhaps even more [1] – synchronously involving large parts of the affected muscle. However, motor unit firing rate during cramp decreases after the initial burst; from about 30 to 17 Hz in the first 10 s [18]. The maximum firing rate observed at the start of a cramp was 89 Hz, faster than during a voluntary contraction but not necessarily incompatible with a central origin [18,25]. Cramps are abolished by nerve block but may still be induced by repetitive nerve stimulation distal to the anaesthetic block. Thus, it has been accepted as likely that cramps usually have a peripheral neurogenic origin. For these studies, a cramp threshold was defined as the minimum frequency of electrical stimulation sufficient to induce cramp [25,26]. However, there is also evidence for an origin at spinal cord level and of spinal modulation of cramp duration and intensity (Fig. 1). Minetto *et al*. [25,26] have compared the electrophysiological features of cramps provoked by peripheral electrical stimulation in a blocked motor nerve with those evoked by stimulating a physiologically normal nerve. They found significant differences concerning cramp threshold (higher when the nerve was blocked), cramp duration, and its mean signal amplitude and motor unit firing rate (always higher when the nerve was intact), meaning that the two experiments elicited unequal cramps. Other reasons to support a central origin are the inhibition of cramp that accompanies

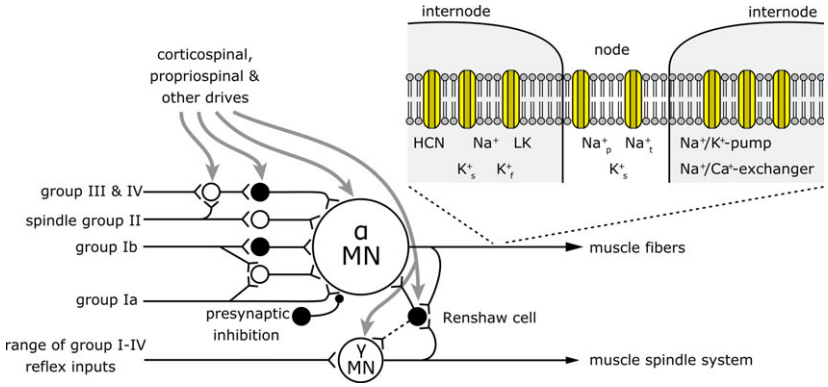

Figure 1 Neurophysiology of muscle cramps. Motoneuronal excitability is controlled by various central and peripheral inputs. It has already been shown that in cramps input to the motoneuron is increased via group IIa, groups Ia and Ib afferents and central efferents. Na^+_p, persistent sodium channel; Na^+_t, transient sodium channel; K^+_f, fast potassium channel; K^+_s, slow potassium channel. (Adapted from Gandevia [77]). [Colour figure can be viewed at wileyonlinelibrary.com]

voluntary contraction of the antagonist muscle or the contralateral homologous muscle [13], enhancement of the H reflex following a cramp [27], depression of the tonic vibration reflex after cramp [18] and inhibition of cramp by stimulation of homologous tendon afferents [17].

In a series of experiments in human subjects suffering from frequent muscle cramps, without other features of neurological disease, Baldissera *et al.* [28] found that cramps could be induced in triceps surae, flexor carpi radialis or flexor digitorum by tendon taps, tendon vibration, or single or short-train stimulation of homonymous 1a afferents. There was stepwise recruitment of additional motor units during repetitive stimulation. The induced muscle cramps could be terminated by a single supramaximal stimulus applied to the mixed motor nerve innervating the muscle, i.e. the posterior tibial nerve innervating triceps surae. The latter effect was thought to result from antidromic stimulation of anterior horn cells and Renshaw inhibition, leading to hyperpolarization of the lower motor neurons (LMN) [29]. Cramping contraction could also be terminated by short electrical volleys applied to skin overlying the muscle, causing inhibition of the soleus H reflex 30–80 and 300 ms after skin stimulation [28]. These results, implying on/off switching of motor unit discharges, have been ascribed to 'bistability' of the cell membranes of discharging motor units [28,29]. During both cramps and myokymic discharges, which involve fewer motor units not all firing synchronously, motor units discharged at 6–12 Hz, in a self-sustaining rhythmic fashion. Rhythmic motor neuron discharges are generated in the soma-dendritic compartment by inward membrane sodium conductance during the after-hyperpolarization potential, a period in which there is normally reduced inward potassium conductance [28,29]. Following an action potential, during the phase of post-discharge restoration of motoneuronal potassium concentration, there is overshoot of the after-hyperpolarization potential (Fig. 1) [30]. Bistability describes neuronal membrane equilibrium existing at two voltage levels, i.e. at the usual negative resting membrane potential (RMP) of about −70 mV and at a higher (more positive) RMP. In the bistability condition, the membrane potential may be less than or greater than threshold. Membrane equilibrium is defined as a state of zero net current flow across the cell membrane, the inward potassium and outward sodium currents being at mutual voltage equivalence [28]. Additional factors that modify membrane conductance, such as 5-hydroxytryptamine and L-3,4-dihydroxyphenylalanine, and calcium flows via activated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) channels may also modify current balance across the motoneuronal membrane. Kiehn and Eken [31] described plateau potentials triggered by short-lasting synaptic input to motoneurons leading to prolonged self-sustained firing at low or higher rates. The plateau potential responsible for repetitive firing in this manner is close to the threshold for motor unit firing, such that afferent input to the motoneuron, e.g. by vibratory excitation of 1a afferents, is sufficient to increase the RMP beyond threshold by causing a reduced net outward current flow insufficient to maintain the normal RMP. A brief excitation can then cause rhythmic, repeated firing [30]. Baldissera *et al.* [28,32] suggested that cramp could be arrested by the combined effect of afferent activity in group Ia and II activity and of pain fibre activation, leading to blockade of the H reflex response pathway and silencing of the continuous motoneuronal discharge (Fig. 1).

Abnormal excitability of peripheral nerve

In addition to spinal mechanisms of cramp, increased excitability of peripheral motor axons, as shown using threshold tracking [33], seems to play a crucial role in cramp in certain neuropathic syndromes associated with cramps (Table 2) [34].

Idiopathic cramp-fasciculation syndrome

There is increased inward rectification in motor axons in idiopathic cramp-fasciculation syndrome (ICFS) [35]. Mathematical modelling suggested that modulation of hyperpolarization-activated cyclic nucleotide-gated channels caused both abnormal gating and rhythm of axonal discharges (described as Hebbian changes), associated with increased excitability and firing rates of motor neurons. Hebb [36] suggested, as a principle of neural activity, that any two cells or systems of cells that are repeatedly active at the same time will tend to become 'associated', so that activity in one facilitates activity in the other, a feature of motor neuronal activity associated with muscle cramping (Fig. 1). Motor unit firing rate during maximal voluntary contraction was increased in ICFS (16.8 Hz with a 47% variance in the interspike interval). A previous study by Kiernan and Bostock [34] did not detect these alterations, probably because they did not use the extended stimulation protocol with prolonged and stronger hyperpolarizing conditioning pulses used by Czesnik and coworkers [35]. Shimatani *et al.* [37] reported a change in slow potassium channel activity in four patients with frequent cramps, but since motor unit multiplets were illustrated in their electromyography (EMG) recordings it is suggested that their patients had neuromyotonia, an autoimmune disorder, rather than ICFS.

Small fibre neuropathies, diagnosed by skin biopsies in the presence of normal sensory and motor conduction, have been reported as a cause in patients with 'idiopathic cramps'.

Neuropathic conditions

Cramps are frequent in polyneuropathies (Table 2), including uraemic [38], diabetic [39], chemotherapy-induced [40] and inherited polyneuropathies [41,42]. Axonal excitability studies in these neuropathies have suggested that this higher prevalence of cramps might be related to increased axonal excitability. In end-stage kidney disease membrane, depolarization may occur due to dysfunctional axonal Na^+/K^+ ATPase [33]. Changes in axonal excitability in diabetic polyneuropathy include impaired axonal Na^+/K^+ ATPase function but also changes in nodal sodium conductances. Oxaliplatin has been shown to cause dysfunctional sodium channels [43–45]. Kanai *et al.* [46] reported an increased strength–duration time constant, reflecting increased sodium channel activity, in a group of patients with cramps associated with Machado–Joseph disease, and observed benefit from mexiletine therapy. In Charcot–Marie–Tooth disease, axonal excitability studies have indicated increased sodium inward currents, increased inward rectification and reduced repolarizing currents [47,48]. Molecular studies in CMT1B mice showed that Nav1.8 is mainly responsible for the enhanced sodium current [49].

However, it has not yet been shown how these changes result in acute neurotoxic effects such as fasciculations, cramps and muscle spasms.

Fasciculation and cramp in ALS

In ALS, fasciculations arise from the motoneuron soma or from ectopic foci in the sprouted motor axonal tree [50]. Fasciculations fire irregularly and, whether arising from motoneuronal firing or from more distal axonal sites, are evidence of increased excitability of the motoneuron and its axon. Fasciculations arising from motoneuron cell bodies originate from the most excitable motoneurons, i.e. those most likely to fire during minimal voluntary activity [50]. Increased motoneuronal excitability implies instability of the motoneuronal cell membrane, due to leakiness

Table 2 Central and peripheral factors associated with muscular cramps and rapid motor unit discharges

Central mechanisms	Peripheral mechanisms	Uncertain mechanisms
Absence of inhibition by muscle pain	Cramps are local to individual muscles, not in a root distribution	Relief of cramp by muscle stretching, antagonist contraction
Loss of modulation of excitability of lower motor neurons	Cramps often occur in part of a muscle	
Centrally acting drugs may be effective	Cramps are associated with axonal hyperexcitability	
	Cramp induced by cutaneous cold stimulation	
	Relief by muscle pressure or heat	
	Relief by sodium channel blockers, e.g. mexiletine	

to potassium or sodium currents or from calcium influx from open NMDA or AMPA channels associated, in ALS, with glutamate toxicity [50,51]. It might also result, in part, from centrally mediated descending excitatory activity in the context of motoneuronal membrane instability [50]. The latter would account for the finding in ALS of simultaneous time-locked fasciculation potentials recorded from adjacent motor units within the same spinal ventral horn segment but innervated by different motor nerves [52,53]. The close relationship of fasciculation to cramp in ALS is consistent with the concept that increased excitability in the LMN occurs as a primary phenomenon [54]. Ultrasound imaging of muscle in ALS has revealed that the spontaneous muscular activation recorded as motor unit fasciculation potentials with focused concentric needle EMG is more widespread than conventionally accepted, involving large volumes of muscle [55].

Myalgia, muscle spasms and cramps in myopathies

Muscle weakness is the typical symptom in myopathies, but patients often also report positive muscle symptoms, especially myalgia, spasms and cramps. It is often difficult for patients to describe exactly the characteristics of cramps, spasms, myotonic contractions or myalgia.

Electromyographic recordings of myopathic muscle cramps do not reveal fasciculations. Thus, the occurrence of fasciculations always indicates a neurogenic disorder as the cause of cramps. Cramp and myalgia are presenting features of the myopathy associated with tubular aggregates in muscle fibres [56]. Muscle cramp is also a feature of Becker muscle dystrophy [57] and of alcoholic myopathy [58]. Cramp may also be a presenting feature of hypothyroidism, associated with fatigue rather than weakness, and with myalgia and a slightly raised blood creatine kinase level [59]. The syndrome responds to thyroid hormone replacement therapy. Hypoparathyroidism is also associated with muscle cramping and with muscle stiffness due to tetany [60].

It is assumed that myopathy-associated cramp and myalgia are associated with muscle fibre membrane dysfunction. This concept has been studied using the velocity recovery cycle of the muscle membrane [61]. In myotonica congenita and myotonic dystrophy types 1 (DM1) and 2 (DM2) the muscle fibre membrane shows delayed repolarization, an observation consistent with impaired chloride conductance in these conditions [62]. In addition, in DM1 sodium channels and Na^+/K^+ ATPase are impaired [63], and in sodium channel myotonia inactivation of sodium channel is abnormally slow [64]. In critical illness myopathy, depolarization of muscle fibre membranes with increased sodium channel inactivation has been reported [65]. Muscle stiffness, pain and contracture in McArdle's myophosphorylase deficiency occur during aerobic exercise. These symptoms are associated with exercise intolerance, fatigue and myoglobinuria. The cramp-like contractures, unlike classical muscular cramp, are electrically silent, since the muscle contracture is metabolically driven by failure of muscle glycogen phosphorylation and of ADP kinetics [66].

Drug-induced cramp

Cramp is an unwanted effect associated with several classes of drug therapy (Table 3), due to diverse mechanisms. Garrison *et al*. [67] studied the incidence of drug-induced cramp in more than 4 million people in British Columbia as shown by rates of prescriptions for quinine, a commonly used remedy at that time. Using this imperfect marker, they found that thiazide diuretics and statins increased the risk for development of cramp, although this risk was less than in direct surveys of cramp related to these treatments. Myotoxicity, with cramp, myalgia, muscle stiffness or weakness, has been reported in 7%–29% of patients taking statins [68,69] and anecdotally described in about 25% of people taking statins. Statin-associated cramp is probably linked to reduced chloride channel conductance in the muscle and impaired mitochondrial oxidative metabolism causing increased lactate levels, reduced ATP levels and decreased calcium pump activity in the sarcoplasmic reticulum [68]. Statin usage is sometimes associated with a painful inflammatory myopathy, distinct from the cramp-myalgia syndrome, due to a statin-induced autoimmune disorder. In general, drug-induced cramps resolve with cessation of therapy, although this may be delayed over several weeks.

Why is cramp painful?

This question has not been adequately addressed in the literature. It is usually assumed that local muscular pain and soreness during and after cramp is due to

Table 3 Drug-induced cramp

Statins	Ciclosporin
Fibrates	Nicotinic acid
Diuretics	Cimetidine
Antiarrythmics	Lithium carbonate
β-adrenergic agonists	Salbutamol
Chemotherapeutic agents	D-penicillamine
Calcium channel blockers (nifedipine)	Gold therapy
Depolarizing muscle relaxants (suxamethonium)	

over-contraction causing damage to muscle fascicles or to ischaemic injury during a long-maintained cramp contraction. The former explanation is more likely since pain is immediate, occurring coincidentally with the forceful muscular contraction. During a cramping contraction, the affected fascicles of the cramped voluntary muscle are tightly contracted and feel hard to the touch, unlike a normal voluntary contraction. In addition, the contraction is maintained involuntarily and cannot be voluntarily relaxed, requiring full passive stretching or elapse of several minutes for full relaxation to occur. The relieved muscle is then painful for up to 24 h. In this respect, persistent local post-cramp pain following spontaneous cramping resembles the pain and stiffness felt in muscles after unaccustomed exercise, as in 'shin splints'. However, in the latter, pain and stiffness probably results from exercise or ischaemia-induced damage to muscle fibres, with oedema, causing activation of nociceptive C fibres within the muscle [70]. Post-cramp muscle pain may indicate failure of the normal protective mechanism whereby a maximal voluntary muscle contraction is inhibited at the point that muscle damage is likely to occur. This normal process could involve Golgi tension receptors or intrinsic muscle nociceptor signalling, causing central inhibition of muscle contraction. However, Golgi tendon organ inhibition was unchanged after static stretch [71], and Graven-Nielsen *et al*. [72] found that muscle pain inhibited force production by a central mechanism.

Management of cramp

Medical interventions to treat or prevent cramp are largely ineffective. Cramp can be alleviated by forced passive muscle stretching, which is effective either simply by 'unlocking' the contracted muscle segment, although this may cause muscle damage and residual tenderness, or by Golgi tendon organ activation leading to inhibition of motor unit firing [72]. Voluntary activation of antagonist muscles can also be effective. Local heat is effective in preventing leg nocturnal muscle cramp in the elderly. There is evidence that local electrical stimulation of muscle with higher susceptibility for cramps leads to higher cramp thresholds in subjects with EAMC [73]. Whether electrical stimulation could also reduce the occurrence of cramps in other medical conditions has to be investigated. Other management strategies include administration of sodium channel blocker drugs, e.g. phenytoin, carbamazepine or mexiletine [74], as prophylactic therapy. However, the efficacy of these drugs is based only on a few case reports [5]. Although quinine is useful in preventing muscle cramps, it is associated with potentially severe side effects including thrombocytopenia and cardiac arrhythmia, and increased mortality [75]. There are also interactions with other drugs via CYP3A4 and CYP450 isoenzymes. Quinine is therefore no longer recommended for use in cramp management. Pickle juice, which contains acetic acid, sipped during a limb cramp reduced cramp duration, probably by an inhibitory oropharyngeal reflex mechanism [76].

Conclusion

Spinal motor system excitation and peripheral axonal membrane disturbances increase susceptibility to cramps (Fig. 1, Table 2). Both central and peripheral categories of causation are relevant. However, the specificity of these factors and the factor(s) leading to their role in the generation of cramping need to be more completely understood. Fuller knowledge might enable mechanism-based treatment both to prevent cramps and to reduce their duration and intensity.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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