How Curiosity Killed the Cramp: Emerging Science on the Cause and Prevention of Exercise-Associated Muscle Cramps

By Bob Murray, PhD, FACSM

Rod MacKinnon and Bruce Bean are experienced sea kayakers who don't allow even blustery winter weather to stop them from long paddling trips off the coast of Cape Cod. Wet suits, cockpit skirts, and constant paddling keep them warm enough in frosty conditions, although they've learned firsthand that muscle cramps are not only a major nuisance but can be life-threatening. Balancing in a needle-thin 17-foot long sea kayak miles from shore as wind, waves, and cold conspire to wrench the paddle from your hands is simply not a good occasion to experience cramps of any sort.

MacKinnon and Bean are long-time friends with overlapping professional interests. Both are neuroscientists, MacKinnon an MD with a professorship at Rockefeller University and Bean a PhD professor at Harvard Medical School. (In 2003, MacKinnon was awarded the Nobel Prize in Chemistry for his research on the structure and function of potassium ion channels.) Both individuals cramped almost simultaneously on a kayak trip; their subsequent conversation naturally turned to the issue of cramping. They were curious about what was known about the cause of muscle cramps and what remedies were available. They dug into the literature and quickly realized that the cause of muscle cramps—as well as effective ways to prevent and treat cramps—were unclear and not thoroughly researched.

Exercise-associated muscle cramps (EAMCs) occur during physical activity and are characterized as "… a sudden, involuntary, painful contraction of a muscle or part of it, self-extinguishing within seconds to minutes and … often accompanied by a palpable knotting of the muscle" (18). EAMCs afflict millions of athletes, workers, soldiers, and fitness enthusiasts, who are forced to alter or cease physical activity when the cramp strikes and then deal with subsequent post-cramp soreness (11).

Although the exact cause(s) are not well understood, numerous factors are thought to influence EAMCs (15), including muscle fatigue, prolonged muscle contractions, muscle damage, restricted muscle blood flow, diabetes, dehydration, and hyperthermia (11). This diversity of the factors associated with triggering EAMCs may explain why a variety of interventions, with mixed results, have been attempted to suppress EAMCs (e.g., hydration, electrolyte replacement, stretching, pickle juice, mustard, etc.) (15).

EAMCs are currently thought to be of neurogenic origin, possibly involving persistent inward electrical currents (PICs) in the dendritic tree of the spinal motor neurons, perhaps promoted by a temporary disruption in the balance of input from muscle spindles and Golgi Tendon Organs, which would normally act to prevent too much tension in the tendon and muscle fibers. In turn, these strong ion currents in the membrane are known to lead to changes in excitability and alter discharge patterns of the motor neurons, sending rapid bursts of action potentials down the axon to cause contraction of muscle fibers (8). In the case of cramp-sensitive skeletal muscles, individual motor nerves in the spinal cord control the contraction of hundreds or—in large muscles such as the quadriceps and gastrocnemius muscles—over one thousand individual muscle fibers. A single motor neuron and the muscle cells it innervates are referred to as a motor unit. Uncoordinated contractions of individual motor units can result in localized fasciculations (twitching) that can sometimes be observed under the skin, especially during or after strenuous exercise. Repeated muscle twitches often occur before the onset of muscle cramps, with simultaneous and continuous discharges of several motor units resulting in full-blown muscle cramps (11,15,18). For many athletes, EAMCs can be an infrequent nuisance during training and competition, while others suffer from debilitating cramps numerous times each week. For those cramp-prone athletes, finding a way to prevent or quickly treat EAMCs can mean the difference between continuing the sport they love or quitting out of frustration.

Evidence for a neurogenic origin of EAMCs includes the observation that cramp-prone subjects have a lower threshold for the electrical stimulation of muscle cramps (1,13,16) and that blocking the motor nerve with certain drugs such as anesthetics decreases or abolishes electrically induced cramping (17). In brief, it appears as though a variety of factors (triggers) may alter normal neuromuscular control, especially so during intense or fatiguing exercise, leading to the development of persistent inward currents in the dendritic field of lower motor neurons sufficient to exceed the excitation threshold of affected

neurons, perhaps coinciding with a simultaneous reduction in inhibitory input from afferent receptors such as Golgi Tendon Organs (18).

Regardless of the trigger for EAMCs (fatigue, dehydration, etc.), if cramps are of neurogenic origin, interventions that decrease persistent inward currents and motoneuron hyperexcitability may prevent EAMCs from occurring or reduce their severity. This concept is supported by the observation that ingestion of pickle juice significantly reduces the duration of electrically induced muscle cramps (14). The consumption of pickle juice (1 ml/kg BW) immediately after the induction of electrically induced cramp of the flexor hallucis brevis muscle of the foot reduced cramp duration compared to the consumption of deionized water. This experiment suggests that the ingestion of pickle juice triggered a neural reflex in the oropharyngeal space that activated spinal inhibitory neurons and reduced alpha motoneuron activity to the cramping muscle, lessening the duration of the cramp.

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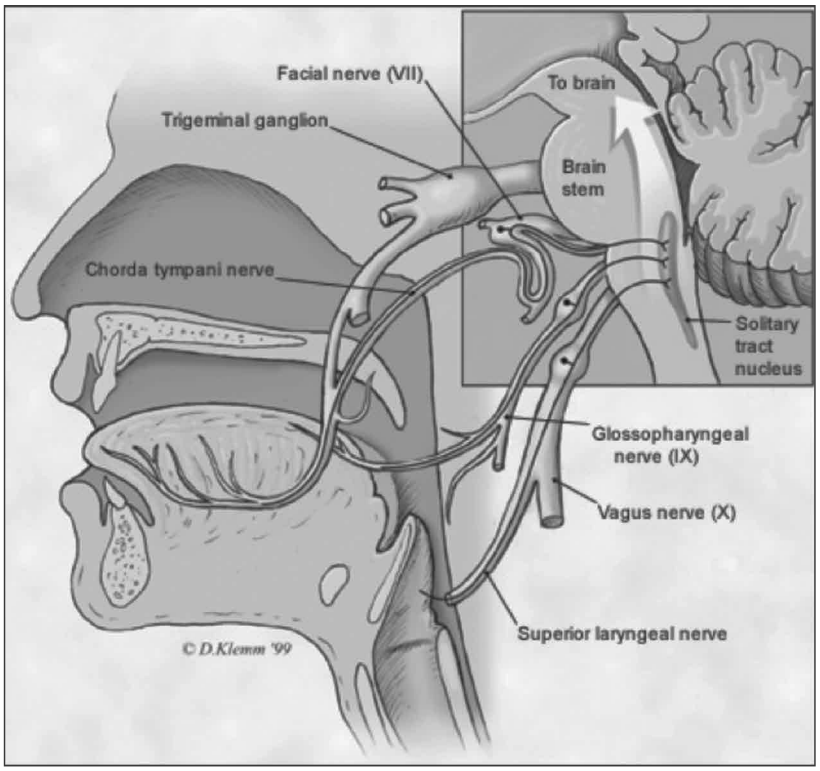
MacKinnon and Bean suspected that a mouth-to-brain-to-muscle mechanism could be effective at preventing EAMCs. They hypothesized that activation of Transient Receptor Potential or so-called TRP ion channels in the sensory nerves of the oropharynx and upper GI tract could reduce the hyperactivity of the motor nerves that sustain a cramp. TRP channels belong to a super-family of membrane channels expressed in many cell types, including sensory nerve cells (19,24) involved in the detection of temperature, tastes, stretch, and pressure as well as noxious and pungent chemical agents (12,20). Specifically, TRPA1 and TRPV1 channels are activated by compounds contained in capsicum, garlic, and other pungent plant extracts (5,19). TRP channels allow cations such as sodium, calcium, and magnesium to pass across membranes and are abundantly expressed in sensory nerves in the oropharyngeal space (see Figure 1), including the trigeminal (V), glossopharyngeal (IX), and vagus (X) nerves that project directly and indirectly to the solitary tract nucleus in the lower brainstem, which in turn has connections to various targets in the brain and brainstem, including the locus coeruleus and the dorsal raphe nucleus. Neural projections from these cell groups extend widely throughout the brain and spinal cord, and activation of these efferent neural circuits in the spinal cord may prevent muscle cramps by decreasing PICs, thereby restoring the normal activity of the motor neurons involved in muscle cramping.

In the hope that their initial observation might benefit athletes with EAMCs and possibly patients with frequent muscle cramps, MacKinnon and Bean started a company* to further their research and combat cramping. There are now several lines of converging evidence to support the concept they developed that TRP channel activation by common natural compounds can prevent and treat muscle cramps by increasing the inhibitory tone in the spinal cord and thereby reduce lower motoneuron hyperexcitability. In experiments reminiscent of electrically stimulating frog muscles in high school biology class, multiple studies of healthy human volunteers using electrically-induced cramps in one foot demonstrated that consumption of a small volume (< 2 oz.) of beverages containing various formulations of TRP channel activators was associated with statistically significant reductions in cramp intensity (EMG area under the curve); in some of these experiments the duration of cramp inhibition was found to last 6-8 hours post-ingestion (9,21-23). The researchers hypothesized that the strong excitatory input produced by TRP channel activators increased inhibitory tone in the spine (e.g., reduced PICs), resulting in a significant diminution of cramp characteristics via inhibition of persistent neural input to the affected muscle. This research has now been presented at the last two American Academy of Neurology (AAN) Annual Meetings (21,23) as well as the 2015 Congress of the European Committee for Treatment and Research of Multiple Sclerosis (ECTRIMS) (9).

Another series of five studies used healthy, but cramp-prone athletes as subjects (n = 139). The athletes consumed a proprietary TRP-activator beverage within 30 minutes of their normal training sessions and recorded the frequency, duration, and pain ratings associated with all episodes of cramping. Other training sessions were completed without any intervention or, with some subjects, using a placebo control beverage. The results consistently showed a reduction in the frequency of EAMCs compared to baseline measures (i.e., cramps were prevented in some subjects.) In addition, the athletes reported a quicker return to training after a cramp episode (10).

Researchers at Penn State University recently presented results showing that consumption of TRP channel activators reflexly decreases neural hyperexcitability, thereby preventing cramping (3). Their volitional, non-electrical cramp paradigm is a closer representation of what athletes experience when cramping during exercise. EMG recordings and other measurements were made before, during, and after each cramp episode. Again, consumption of the TRP-activator beverage significantly reduced the EMG area under the curve, consistent with inhibition of motoneuron activity in the cramped muscle. In addition, consumption of the beverage was associated with lower post-cramp muscle soreness ratings in the 20 minutes following the cramp (3), a response possibly due to the reduced intensity and duration of cramp contraction and related pain rather than cramp-induced muscle damage.

Figure 1: *A simple schematic of the sensory nerves innervating the oropharyngeal space.*



* FlexPharma, Inc.

It is possible that consuming a beverage that sufficiently activates TRP channels might not only prevent muscle cramps but also improve exercise capacity.

Several lines of research are now being pursued to better understand the cause of EAMCs and the pathophysiological conditions that precede the onset of overt muscle cramping. As pointed out, fasciculations or "muscle twitches" are commonly observed before overt cramping. How does the uncontrolled discharge pattern of a single motor neuron suddenly reach a "flashpoint" to expand to neighboring motor neurons in the spinal cord? Why is this phenomenon usually limited to a single muscle? What are the mechanisms that prevent the expansion and keep a cramp localized to a single muscle rather than spread ephaptically, directly across adjacent nerve fiber membranes, to neighboring muscles? Studies are underway to address these questions and understand the immediate and delayed consequences of muscle cramping, as well as what other performance and recovery benefits TRP activation might have for an athlete. A particular focus of this research is the relationship to immediate and delayed onset muscle soreness, muscle damage and inflammation, and the important functional aspect of motor recovery. This promising line research may provide a better understanding of the neural mechanisms that degrade muscle performance acutely and how the activity of certain neural circuits may positively impact neuromuscular performance such as exercise capacity immediately following treatment intervention and over time. In this respect, TRP channel activation may have many beneficial consequences for athletes and as well as for patients with neuromuscular disease. It is possible that consuming a beverage that sufficiently activates TRP channels might not only prevent muscle cramps but also improve exercise capacity. In fact, previous research has demonstrated performance improvements such as increased cycling power output associated with various types of oropharyngeal stimulation (2,4,6,7,25).

Practical Implications

Frequent cramps can be a soul-crushing experience for athletes who pour their hearts and souls into training, only to be sidelined by an untimely cramp. Finding effective prevention is a welcome relief. For cramp-prone athletes, there are a few scientifically proven interventions on the market nowadays that prevent or treat cramps. Other interventions which have been used to treat muscle cramps include intravenous electrolytes, apple cider vinegar, mustard, sedatives, anti-seizure medications, and even pinching the upper lip, but evidence of reliable efficacy is lacking in most cases. Athletes are always well-advised to follow current guidelines for hydration and nutrition to reduce the fatigue-induced risk of cramping. Stretching a cramped muscle is usually effective at releasing the cramp by activating the afferent inhibitory influence of Golgi Tendon Organs, but athletes don't want to have to stop, preferring cramp prevention over treatment.

Bob Murray co-founded the Gatorade Sports Science Institute (GSSI) and served as its director from 1985 to 2008. After departing GSSI, Bob founded Sports Science Insights, LLC, where he consults for Flex Pharma, Inc., to identify qualified university scientists to conduct related research projects and help in research design and the interpretation of results.

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