Transient receptor potential channels and exercise-associated muscle cramping: A tale of multiple complexities

M P Schwellnus, MBBCh, MSc (Med), MD, FACSM [a]
M D Hoffman, MD, FACSM[b]

[a] Professor of Sport and Exercise Medicine, Faculty of Health Sciences, Department of Orthopedics, Section Sports Medicine, University of Pretoria, South Africa, Sports Campus, Burnett Street, Hatfield, Pretoria 0020, South Africa South Africa
[b] Chief of Physical Medicine & Rehabilitation, Department of Veterans Affairs, Northern California Health Care System, and Professor of Physical Medicine & Rehabilitation, University of California Davis Medical Center, Sacramento, CA, United States

Corresponding author for proof and reprints:
[a] Martin P. Schwellnus, Director: Sport, Exercise Medicine and Lifestyle Institute (SEMLI), Faculty of Health Sciences, University of Pretoria, South Africa, Sports Campus, Burnett Street, Hatfield, Pretoria 0020, South Africa
Telephone: -27-12-420 6057 Fax number: -27-12-362 3369
Email: mschwell@iafrica.com

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We, the authors, confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Introduction

In an important study published in 2010, Miller et al, showed that the duration of muscle cramping was reduced by administration of oral pickle juice immediately following electrically induced muscle cramps in hypohydrated humans (1). The authors concluded that this effect could not be explained by rapid restoration of body fluids or electrolytes, and suggested it reflected a neutrally-mediated reflex originating in the oropharyngeal region and inhibiting the firing of alpha motor neurons of the cramping muscle. This observation led to the hypothesis that the mechanism by which pickle juice attenuated exercise-induced muscle cramping (EAMC) may involve stimulation of transient receptor potential (TRP) channels. These TRP channels have been found in the upper gastrointestinal tract (GIT), including the oropharyngeal region. In this editorial we explore some of the methodological considerations related to a novel approach to study EAMC in the laboratory, EAMC as a more complex clinical entity than previously considered, and the complexity of TRP channels and their possible role in EAMC.

Methodological considerations related to a novel approach to study EAMC in the laboratory

In this issue, Craighead et al (2)describe a new laboratory approach to cramp induction that seems more relevant to the study of EAMC than electrically induced muscle cramping. This could generate new opportunities for expanding our understanding of muscle cramping in general, and specifically EAMC. The authors report that the ingestion of 50ml of a drink containing naturally occurring transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential Ankyrin 1 (TRPA1) agonists attenuated some characteristics of cramping when compared with a vehicle control drink. Apparently healthy human participants performed an isometric maximum voluntary contraction of the ankle plantar flexor muscles, while in a shortened position, until a cramp was induced. If no cramp was induced after 90 seconds, the contraction was repeated after a 10 minute rest period up to a maximum of 5 cycles. TRP agonist

ingestion increased the duration of an isometric contraction cycle before a cramp was induced, decreased EMG intensity-duration area under the curve during the cramp, increased contraction force before the onset of cramping, and decreased post-cramp soreness, while there was no effect on EMG intensity-duration area under the curve during pre-cramp isometric contraction and duration of muscle cramping.

There are several methodological considerations related to this study. The precise content and dosage of the ingested TRP agonist mixture is not well described – it is only indicated to have "included one or more of the following" - up to 38mg capsicum, up to 500mg cinnamon, and up to 750mg ginger. There were large inter-individual variations in responses among the participants for all the cramp outcomes studied, and one–tailed t-tests were used to assess differences between active and control interventions without indication that the data were normally distributed. It is also worth noting that all participants ultimately cramped with both the active and control interventions. Another important observation is that, although the time to onset of cramping during the one maximum voluntary isometric contraction cycle that induced the cramp was reported, the number of maximum voluntary isometric contraction / rest cycles that were required to induce a cramp were not reported. This information is very important because multiple attempts could result in progressive muscle fatigue, which could alter the time of onset to cramping during the single isometric contraction cycle and result in misleading conclusions. Finally, although EMG activity was measured in 4 muscles, including tibialis anterior (presumably as a control), it is not clear for which of these four muscles the EMG data are reported, and how the EMG responses might have differed among muscle groups. These considerations should be addressed in future studies, and the data presented in this study should be interpreted with these considerations in mind.

Complexities related to the etiology, pathophysiology, clinical presentation and treatment of EAMC

In the last decade, several researchers conducted studies that deepen our understanding of muscle cramping in general, and EAMC specifically. An important fact is that muscle

cramping is a clinical feature of a number of inherited or acquired chronic neuromuscular conditions and other chronic diseases, and is also a negative side effect of many drugs or toxins (3). It can occur at rest, during sleep and during exercise.

EAMC remains one of the most common clinical syndromes for which athletes seek medical care, particularly at endurance events (4) (5). Historically, EAMC was considered, rather simplistically, as a single entity caused by dehydration and electrolyte imbalances. We challenged this hypothesis in 1996 (6) and presented an alternate hypothesis for the development of EAMC in 2009 (7). A key component in the pathophysiology of EAMC is the development of muscle fatigue. The clinical presentation of EAMC therefore also represents a spectrum of conditions ranging from 1) primary fatigue-inducing EAMC, 2) secondary EAMC as a result of underlying injury, chronic disease or medication (drug) use, or 3) a combination of primary and secondary factors. It is likely that all of these factors can alter spinal motor neuron control during exercise, and there is also now general agreement that the final common pathophysiological pathway for EAMC is altered neuromuscular control at the spinal level resulting in sustained motor neuron hyperexcitability due to multiple causes (8) (9) (10). In support of this, we recently reported an association between several chronic diseases, medication use and injury history in large cohorts of endurance runners with EAMC (11) (12) (13). Therefore, the etiology, pathophysiology, diagnosis, treatment and prevention of EAMC is complex, and it is imperative that the clinician conduct a full diagnostic workup in patients with EAMC and then follow this with an appropriate treatment strategy that addresses underlying cause(s). A single treatment modality or prevention strategy cannot be expected to be effective for all athletes with EAMC.

Complexities related to TRP channels and exercise

A further area that deserves some discussion, to place this study into context, is the complexity of the role of TRP channels in general human physiology and exercise physiology. TRP channels were discovered more than 20 years ago in flies, and are atypical ligand-gated cation channels that have now been shown to have numerous

functions in the physiology and pathophysiology of many organisms, including humans (14). The TRP superfamily is divided into several sub-families of which the TRPV and TRPA are two sub-families. The members of the TRP channel superfamily have several distinct, unique and very complex regulatory, biophysical and pharmacological properties, and their role in human physiology and pharmacology were recently reviewed (14). TRP ion channels function as molecular detectors of physical stimuli, with potential roles in numerous processes and systems including thermoregulation (15), the inflammatory and immune systems (16), the broncho-pulmonary system (17), whole body metabolism and glucose homeostasis (18), cancer and tumorigenesis (19), pain (20) and GIT function (21). Three TRP family subtypes (TRPV1-4, TRPA1, and TRPM8) are expressed in nociceptors in the skin and GIT, where they act as transducers for signals from temperature, chemical and mechanical stimuli. Activation, sensitization and desensitization of these channels are involved in nociceptive, inflammatory and neuropathic pain and there are numerous exogenous agonists, endogenous agonists, antagonists and intracellular modulators of the TRP family subtypes (TRPV1-4, TRPA1, and TRPM8) of which capsicum, cinnamon, and ginger only represent a small group of potential agonists.

TRPV1 activation during exercise is very complex and may influence a number of physiological responses during exercise including physical performance, thermoregulation, metabolism, the cardiovascular response to exercise, inflammation, water and electrolyte balance, and oxidative capacity of the muscle (15). The role of TRP channel activation (by agonists such as capsaicin), desensitization through single or repeated exposure to agonists, or suppression by antagonists during rest and exercise is very complex and not well understood. Therefore, the effects of administration of a single oral solution containing a few TRPV1 agonists during rest and exercise requires much more in-depth study before it can be advocated as a specific treatment for conditions that can present as EAMC. Recently, expressions and functions of TRPV1, TRPA1, and TRPM8 in primary afferent nerves in the GIT have also been reviewed. Again, the activation (for example by capsaicin), desensitization, or blocking (by antagonists) of these TRP channels in the GIT, and the subsequent effects on the nervous system are very

complex, not well understood, and require further research (22).

Summary and conclusion

In summary, our current understanding is that EAMC is a complex clinical syndrome that is associated with multiple causes. The complex role of TRP channels in general human physiology and exercise physiology is also not well understood, and requires further research. The study in this issue is a contribution to further advancing our understanding of the complex nature of both EAMC and TRP channel physiology. It is likely that further research will identify specific causes and the related pathophysiology of EAMC in athletes. As in all areas of clinical medicine, prevention and treatment should ultimately be directed toward the underlying cause(s), even when a given symptomatic treatment may be effective in some cases.

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