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EDITORIAL

Potassium effects on skeletal muscle contraction: are potassium-metabolic interactions required for fatigue?

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Potassium (K^+) disturbances across the sarcolemma during exercise or stimulation have long been postulated to contribute to skeletal muscle fatigue, i.e., an acute reduction of muscle force or power output (Cairns and Lindinger 2008; Hostrup et al. 2021). Never-the-less it has also been proposed that K^+ is not normally a factor in fatigue during exercise in vivo due to compensatory physiological processes which protect against detrimental K^+-effects (Allen et al. 2008). The extensive review article by Renaud and colleagues in this issue of the *Eur J Appl Physiol* (Renaud et al. 2023), within the present series of a century of exercise physiology, revisits the role of K^+ in fatigue. Over the past 30 years there have been notable advances in understanding about the physiology of K^+-effects on cellular processes, K^+-ionic-interactions, muscle chloride (ClC-1) channel function, ATP-dependent K^+ (K_{ATP}) channel function, sodium–potassium-(Na^+-K^+) pump regulation, and importantly K^+-metabolic interactions. Based on some of these studies the authors provide a new perspective on the role of K^+ for skeletal muscle function during exercise. They remind us and highlight that K^+ can have both protective and/or detrimental effects on muscle function through interactions with other ionic changes. In particular, they emphasise that the K^+-metabolic interactions that occur during latter stages of fatiguing exercise are likely contributors to any force reduction, which then protects against damaging effects of severe ATP depletion.

The current line of thought on how K^+ participates in muscle fatigue is as follows (Cairns and Lindinger 2008; Hostrup et al. 2021; Renaud et al. 2023). Repeated contractions result in K^+ efflux across the sarcolemma, including transverse-tubular system membranes, via various K^+ channels (delayed rectifier K^+-channels, K_{ATP} channels), leading to a raised extracellular [K^+] ($[K^+]_o$) and lowered myoplasmic [K^+] ($[K^+]_i$), i.e., a rundown of the trans-sarcolemmal K^+-gradient. Such K^+ disturbances evoke depolarisation of the sarcolemma since the K^+-equilibrium potential (which is lowered) is the main determinant of resting membrane potential (resting E_M). Depolarisation is then thought to inactivate voltage-dependent Na^+-channels resulting in smaller Na^+ currents. Such effects then (i) diminish action potential amplitude which reduces Ca^{2+} release from sarcoplasmic reticulum, and/or leads to a failure of action potential propagation along the sarcolemma and (ii) diminish subthreshold excitatory currents which fail to trigger action potentials either in quiescent fibres or during a train of stimuli. In consequence, K^+-effects on contraction are best described by the peak tetanic force-resting E_M relationship, as illustrated for extensor digitorum longus muscles of mice (Fig. 1) (Cairns et al. 2022). This relationship shows that a large reduction of K^+-gradient or large depolarisation is needed to overcome a safety margin range for resting E_M before peak tetanic force plummets dramatically over a narrow (~5 mV) critical range of resting E_M. Hence for K^+ disturbances to be the sole contributor to fatigue an extensive K^+ shift is necessary; several authors consider that K^+ changes in isolation are insufficient to cause much fatigue (Allen et al. 2008; Renaud et al. 2023). Importantly, several factors can modulate this relationship and this Editorial focusses on the three main themes proposed by Renaud and coworkers which influence this relationship.

Firstly, when non-fatigued muscles are exposed to moderately raised $[K^+]_o$, e.g., increase from 4 to 7–10 mM, or with brief time exposures to higher $[K^+]_o$, then smaller depolarisations of resting E_M transpire together with a potentiation of submaximal forces (Cairns et al. 2022; Pedersen et al. 2019; Renaud et al. 2023). Such force potentiation features only with twitch and submaximal frequency stimulation to evoke an increased power (Pedersen et al. 2019). The underlying

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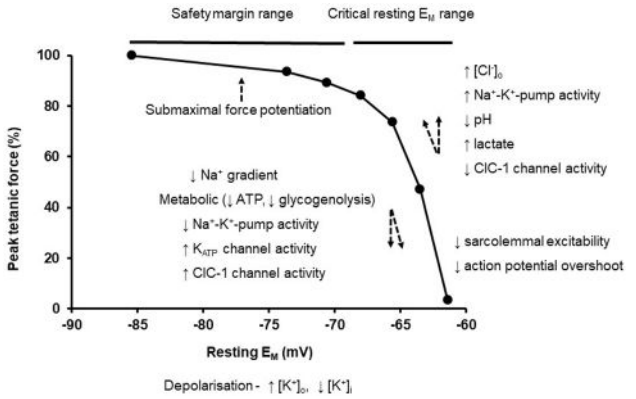

Fig. 1 The peak tetanic force-resting E_M relationship for mouse extensor digitorum longus muscles in vitro. This relationship depicts that progressive changes of sarcolemmal K^+-gradient, i.e. ↑$[K^+]_o$ and/or ↓$[K^+]_i$, lead to an increasing depolarisation whereby peak force is first largely maintained (safety margin range) and then falls abruptly and massively (critical resting E_M range). With smaller depolarisations there is submaximal force potentiation to aid maximal force maintenance. Factors identified to the right of the relationship (top) restore or maintain peak force (i.e., force increase at each resting E_M, or repolarisation upwards along the relationship); factors to the left of the relationship (bottom) cause a reduction of force (i.e., force decrease at each resting E_M, or further depolarisation downwards along the relationship). The latter scenario evokes smaller action potentials and inexcitability which potentially lead to fatigue

processes are related to increased Ca^{2+} release from the sarcoplasmic reticulum (Pedersen et al. 2019; Hostrup et al. 2021), which also adequately explains the lack of effect on maximal tetanic force, since troponin is likely saturated with Ca^{2+}. This potentiation process likely contributes to force maintenance in the safety margin range (Fig. 1). Whilst the mechanisms underpinning this force augmentation are still not fully understood it is clear that smaller K^+ changes are beneficial for submaximal contractions, along with improving muscle blood flow, heart rate, ventilation, and neuromuscular transmission (Renaud et al. 2023).

Secondly, raised $[K^+]_o$ to higher levels are not always depressive for muscle contractile performance since very large K^+-induced depolarisations are needed to reach the critical resting E_M range for the massive decline of force (Fig. 1). Renaud and colleagues mention several interacting aspects that may convey this protection (Fig. 1, right side top). (i) A normal high extracellular chloride concentration $[Cl^-]_o$, and hence high Cl^--equilibrium potential, stabilises the resting E_M thereby resisting the K^+-induced depolarisation which occurs more slowly and to a lesser extent (Cairns and Lindinger 2008; Hostrup et al. 2021). (ii) Several factors can stimulate Na^+-K^+-pump activity i.e., raised myoplasmic $[Na^+]$, catecholamines, calcitonin gene-related peptide (released from nerve terminals), amylin (released from the pancreas) and pump translocation to the surface sarcolemma (Hostrup et al. 2021) which together protect against detrimental K^+-effects. Increased Na^+-K^+-pump activity yields protection via an enhanced outwards electrogenic current or restored K^+-gradient, both of which cause repolarisation, or an increased Na^+-gradient across the sarcolemma. Such effects cause an upwards or leftwards shift back along the force-resting E_M relationship to restore force. (iii) Even in the presence of an extensive K^+-induced depolarisation there are beneficial effects mediated by stimulation-induced increases of lactate, acidosis, or protein kinase-C that resist depressive K^+-effects on force via reducing ClC-1 channel opening and hence a partially lowered Cl^- conductance (Hostrup et al. 2021; Nielsen et al. 2017). With lesser ClC-1 channel opening there is attenuated subthreshold inhibitory currents, which enables the excitatory subthreshold Na^+ current to bring the sarcolemma to threshold to trigger action potentials and overcome K^+-induced inexcitability (Nielsen et al. 2017).

The K^+-induced potentiation of submaximal forces and defence against detrimental K^+-effects mediated through high $[Cl^-]_o$, increased Na^+-K^+-pump activity, and decreased ClC-1 channel activity are all active processes in the safety margin range (Fig. 1) so that potentially negative K^+-effects do not become that bad. Clearly K^+ is initially protective or at least not detrimental for muscle contractile force. These combined physiological effects occur either early during intense exercise or with lower intensity exercise and constitute the Phase I as identified by Pedersen and coworkers (Leermakers et al. 2020; Nielsen et al. 2017).

Thirdly, when the exercise is more intense and prolonged then larger K^+ disturbances manifest together with a substantial metabolic stress. According to Renaud et al. (2023) this coincides with the Phase II as described by Pedersen's team (Leermakers et al. 2020; Nielsen et al. 2017). In this scenario, a muscle energy deficit, i.e., ATP decline, occurs, which may also be linked to diminished glycogenolysis/glycolysis, and in consequence this influences several processes which interact with K^+-effects i.e., K^+-metabolic interactions (Leermakers et al. 2020). Renaud and coworkers emphasise that such localised ATP depletion would (i) reduce Na^+-K^+-pump activity (hence cause further depolarisation together with a lowering of the Na^+-gradient), (ii) increase K_{ATP} channel activity and (iii) increase ClC-1 channel activity. The latter two metabolic effects on K_{ATP} and ClC-1 channels augment inhibitory currents so that some fibres do not have sufficient subthreshold current to trigger action potentials, and even once triggered evokes only smaller amplitude action potentials. Hence such K^+-metabolic interactions cause a downwards or rightwards shift along the peak tetanic force-resting E_M relationship leading to less Ca^{2+} release from sarcoplasmic reticulum and lowered force production. Clearly this suggests that K^+-metabolic interactions are a likely contributor to lower force especially during the critical resting E_M range (Fig. 1).

Despite this, it should be noted that whenever there is K^+ efflux during action potentials there is also Na^+ influx (leading to a reduced Na^+-gradient) and the combined K^+ and Na^+ disturbance has powerful detrimental effects on action potentials to shift the peak tetanic force-resting E_M relationship downwards and thus also cause fatigue.

In conclusion, there are many putative factors that may contribute to fatigue depending on the exercise regime or fatigue model employed (Allen et al. 2008; Hostrup et al. 2021). For K^+ to be involved in fatigue the perspective of Renaud and coworkers is that the occurrence of a metabolic stress is needed to amplify detrimental K^+-effects, whenever exercise-induced K^+-disturbances occur, and thereby contribute to force loss during fatiguing exercise.

Declarations

Conflict of interest The author declares no competing interests.

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