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INVITED REVIEW

Regulation of muscle potassium: exercise performance, fatigue and health implications

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Abstract

This review integrates from the single muscle fibre to exercising human the current understanding of the role of skeletal muscle for whole-body potassium (K^+) regulation, and specifically the regulation of skeletal muscle [K^+]. We describe the K^+ transport proteins in skeletal muscle and how they contribute to, or modulate, K^+ disturbances during exercise. Muscle and plasma K^+ balance are markedly altered during and after high-intensity dynamic exercise (including sports), static contractions and ischaemia, which have implications for skeletal and cardiac muscle contractile performance. Moderate elevations of plasma and interstitial [K^+] during exercise have beneficial effects on multiple physiological systems. Severe reductions of the trans-sarcolemmal K^+ gradient likely contributes to muscle and whole-body fatigue, i.e. impaired exercise performance. Chronic or acute changes of arterial plasma [K^+] (hyperkalaemia or hypokalaemia) have dangerous health implications for cardiac function. The current mechanisms to explain how raised extracellular [K^+] impairs cardiac and skeletal muscle function are discussed, along with the latest cell physiology research explaining how calcium, β-adrenergic agonists, insulin or glucose act as clinical treatments for hyperkalaemia to protect the heart and skeletal muscle in vivo. Finally, whether these agents can also modulate K^+-induced muscle fatigue are evaluated.

Keywords Skeletal muscle · Cardiac muscle · Hyperkalaemia · Hypokalaemia · Na^+/K^+-ATPase

Abbreviations

ATP	Adenosine triphosphate
$[Ca^{2+}]_i$	Intracellular calcium concentration
cAMP	Cyclic adenosine monophosphate
$[Cl^-]_i$	Intracellular chloride concentration
ClC-1	Skeletal muscle sarcolemmal chloride channel
ECFV	Extracellular fluid volume
ECG	Electrocardiogram
ICFV	Intracellular fluid volume
K_{ATP}	ATP-dependent potassium channel
$K_{Ca1.1}$	Delayed rectifier potassium channel
K_{ir}	Inward rectifier potassium channel
$[K^+]_a$	Plasma arterial potassium concentration
$[K^+]_i$	Intracellular potassium concentration
$[K^+]_I$	Interstitial potassium concentration
$[K^+]_o$	Extracellular potassium concentration
$[K^+]_v$	Plasma venous potassium concentration
M-wave	Compound extracellular muscle action potential
$[Na^+]_i$	Intracellular sodium concentration
NKA	Na^+/K^+ ATPase (sodium–potassium pump)
NKCC	Na^+-K^+-$2Cl^-$ cotransporter (sodium–potassium chloride cotransporter)
Resting E_M	Resting membrane potential
RPE	Rating of perceived exertion
TBW	Total body water
T-system	Tubular system
VO_2peak	Peak oxygen consumption

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Introduction

In the year 2000, the comprehensive and excellent review on muscle potassium (K^+) was published (Sejersted and Sjøgaard 2000). As in the years leading to the publication of this review, the past 2 decades has also seen the publication of numerous basic, applied and clinical research papers that span research performed using subcellular approaches, e.g. skinned fibres, patch clamp, through to single intact fibres, isolated muscle preparations in vitro, perfused muscle in situ, and the exercising human. The aim of the present review is to integrate the findings of recent in vitro research with human exercise performance and clinical research to provide a synthesis of our current understanding of the regulation of muscle K^+ for exercise performance, fatigue and health.

What K^+ is and why K^+ is needed in the body

Potassium is a positively charged element (an electrolyte/ion, specifically a cation) ubiquitously found in the body fluid compartments of most animals, plants and other life forms (Demigné et al. 2004). It is readily obtained from dietary meat and plant products (Hamidi et al. 2011; Mangels 2014). Nonetheless, there are situations when K^+ supplements are needed to maintain or achieve a proper balance of K^+ within the body. Notable amongst these situations is diuretic therapy that results in elevated renal excretion of K^+ (Stone et al. 2016). At other times, there is a need to eliminate excess K^+, taken into the body through ingestion or injection, or through failure of K^+ regulatory organs such as the kidneys and skeletal muscle.

While K^+ is found in body fluids it is not uniformly distributed. There is a highly regulated distribution of K^+ at multiple levels including the intestinal epithelium (regulating intestinal transport and absorption), the plasma membranes of all cells (regulating both extracellular and intracellular K^+ concentrations, i.e.$[K^+]_o$ and $[K^+]_i$, respectively), renal epithelial cells (regulation of whole-body balance of K^+) and sweat glands (regulation to conserve K^+ within the body) (McDonough and Youn 2017; Youn 2013). Potassium is also regulated within cells, notably at the surface membrane and also at mitochondrial membranes and membranes of other intracellular organelles (DiFranco et al. 2012; Lindinger 2005). This high level of regulation implies unique physical and chemical attributes of the cation, and the effects of its concentration or activity, with respect to biological functions within the body. For example, is K^+ sensed by receptors (or binding sites) and if so, how is it sensed? The quick answer is that $[K^+]$ appears to be sensed indirectly (Landowne et al. 1975; Ogielska and Aldrich 1999) and possibly directly (DiFranco et al. 2015b; Hakimjavadi et al. 2018) by sensors on the surface of many types of cells. Therefore, there must be graded responses that depend on concentration and perhaps on the rate of change of $[K^+]$. What is special about K^+ with respect to its ability to being sensed? For the purposes of comparison, it is beneficial to examine two other univalent ions that are regulated together with K^+, i.e. sodium (Na^+) and chloride (Cl^-). The molecular mass of K^+ is 42 g/mol, while those for Na^+ and Cl^- are 23 and 35 g/mol, respectively. When in solution, these ions attract molecules including H_3O^+ (hydronium ion), OH^- (hydroxyl ion), H^+ (hydrogen ion) and H_2O (water). Hence, in physiological solution, they have a hydrated radius that plays a major role in the ability of cell ion transport systems to discern between K^+ and Na^+, as both ions have the same charge and similar molecular mass (Conway 1981; Landowne et al. 1975). Water molecules in the hydration shell of K^+ are somewhat disordered compared to those hydrating a Na^+ and tend to incline their dipole moments tangentially to the hydration sphere (Mancinelli et al. 2007). Chloride, on the other hand, in addition to being negatively charged, i.e. an anion, forms hydrogen-bonded bridges with water molecules and are readily accommodated into the H-bond network of water. The hydrated radii of K^+, Na^+ and Cl^- are 3.3 Å, 3.55 Å and 3.3 Å, respectively (Conway 1981). Membrane receptors are, therefore, able to sense and respond primarily to those ions for which they have been designed to be responsive. For example, the fact that potassium channels are sensitive not only to K^+, but also to $Rb^+ > Cs^+ > Na^+$ in general has been exploited by researchers studying K^+ movement (Lam et al. 2014).

The $[K^+]$ in plasma at rest ranges from 3.5 to 5 mM and within cells, i.e.$[K^+]_i$, ranges from 60 to 160 mM, depending on cell type. The primary effector of the transmembrane $[K^+]$ gradient was shown to be the sarcolemmal Na^+/K^+ ATPase (NKA), discovered and characterised by Jens Skou over the period 1957–1962 and for which he was awarded the Nobel Prize in chemistry in 1997. Notably, Skou (1962) demonstrated the inhibition of the NKA by the glycoside ouabain. The regulation of this important membrane protein is complex and affected by catecholamines, insulin, contractile activity, membrane potential (resting E_M), intracellular $[Na^+]$ ($[Na^+]_i$), and several other molecules (see Clausen 2000, 2003; Pirkmajer and Chibalin 2016).

The regulation of K^+ implies that sensors exist on or in cell membranes that detect the presence of $[K^+]_o$ and possibly $[K^+]_i$. An external sensor for $[K^+]_o$ on the NKA (DiFranco et al. 2015b; Hakimjavadi et al. 2018), indeed regulates NKA activity. It is unknown if another sensor detects when $[K^+]_i$ is adequate. Many membrane channels,

including outward and inward rectifier K^+ channels, are sensitive to changes in resting E_M. The resting E_M is largely determined by, but is typically greater (i.e. more polarised), than the equilibrium (Nernst) potential for K^+, as described quantitatively by the Goldman–Hodgkin–Katz equation (Cairns and Lindinger 2008; Lindinger 2005); therefore, there appears to be a dynamic, sensitive microdomain feedback between intracellular/extracellular $[K^+]$, resting E_M and K^+ channel opening. The key point is that the regulated $[K^+]_i$ is 15–40 times greater than in extracellular fluids. The resultant $[K^+]$ difference across cell membranes determines the K^+-equilibrium potential (E_K) that is crucial for cell function. The functions of the intra- to extracellular $[K^+]$ gradient include secretion of urine (renal epithelial cells), secretion of sweat (sweat gland epithelial cells), signal transmission, and action potential generation and propagation (neurons and muscle cells, and hence brain, cardiac and skeletal muscle function), as well as a myriad of transport functions in various epithelial cells and cellular organelles throughout the body.

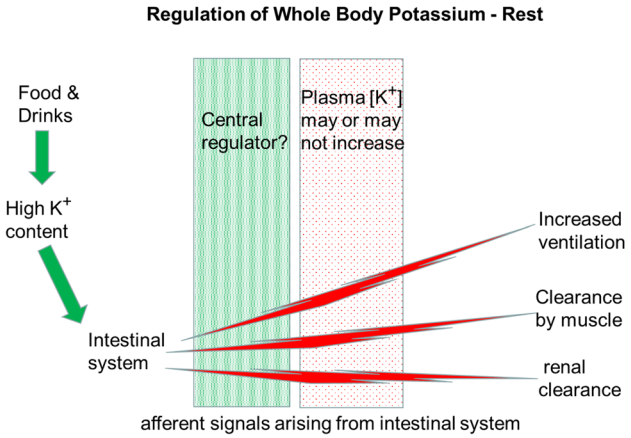

Fig. 1 Schematic representation of the main aspects of regulation of whole-body K^+ balance at rest. There is remarkably little oscillation of plasma $[K^+]_a$ when ingesting many high K^+ drinks and foods. There is a feed-forward system to the kidneys (and possibly skeletal muscle) to effect renal K^+ clearance when high $[K^+]$ is sensed in the small intestine (Youn 2013), although unclear if this involves a central integrator. Elevated plasma $[K^+]_a$ stimulates ventilation (Paterson 1997), likely through involvement of a central regulator. Elevated plasma $[K^+]_a$ stimulates extraction of K^+ by tissues, especially skeletal muscle

Overview of whole-body K^+ balance

The reader is referred to the review by McDonough and Youn (2017). We use 70 kg as the mass of an average western male of normal body composition to describe K^+ distribution—the values can be linearly scaled to any body mass for men and women as there are no known sex differences with respect to hydration and K^+ distribution. Intracellular fluid volume (ICFV) is ~ 57% of total body water (TBW) and extracellular fluid volume (ECFV) is ~ 43% of TBW. Since the TBW is ~ 72% of body mass then the ICFV is ~ 24L and ECFV ~ 18L, with TBW of ~ 42L (ICRP 2002). The average $[K^+]$ within cells is 125 mM (Kowalchuk et al. 1988; Lindinger and Grudzien 2003; Lindinger and Heigenhauser 1987), therefore, giving about 3.0 mol of K^+ within cells and 0.07 mol outside of cells. There is also K^+ 'stored' within bone and cartilage (0.25 mol) that is slowly exchangeable with extracellular K^+ but can serve as a 'reservoir' of K^+ in times of K^+ depletion (Williams and Leggett 1987). The body, therefore, has about 3.3 mol of K^+—based on molecular mass and this is equal to 140 g (ICRP 2002). The majority of K^+ in the body is found in skeletal muscle (68%), bone (7.5%), blood contents and spleen (3.7%), liver (3.3%), blood vessels (epithelium and smooth muscle cells—3.2%), central nervous system (2.8%), and cardiac muscle (0.6%) (Willliams and Leggett 1987).

Whole-body K^+ balance at rest (Fig. 1) is a function of dietary intake, intestinal absorption and excretion and renal secretion (McDonough and Youn 2017). With increased muscular activity and sweating, then cutaneous secretion of K^+ onto the skin occurs (Baker and Wolfe 2020). The level of chronic physical activity/inactivity also markedly affects the distribution of K^+ in soft tissues, especially skeletal muscle (Deogenes et al. 2007; Wyckelsma et al. 2019; Zorbas et al. 2009). Losses may also occur when the intestinal system is 'leaky' (Agarwal et al. 1994; Priyamvada et al. 2015). The main sources of dietary K^+ are meats and dairy products, and plant products including legumes, vegetables, potatoes and fruit (Hamidi et al. 2011; Mangels 2014). Dietary K^+ loads can result in locally high $[K^+]$ in the gut, portal circulation and liver. There also appears to be K^+-sensitive sensory mechanisms within the liver/portal circulation (Gumz et al. 2015) and or gut which feeds forward to signal K^+ retention or clearance by the kidneys (Youn 2013). These mechanisms appear to be important in attenuating the hyperkalaemia and attendant risk of cardiac arrhythmias that are sometimes associated with rapid ingestion of K^+ rich meals and solutions (Lindinger et al. 1999a, b; Youn 2013).

Intestinal system

With self-selected diets, the daily K^+ ingestion in foods averages 2.8 g/day, of which 85% is absorbed by the intestinal tract over the wide range of intakes (Holbrook et al. 1984). Average urinary excretions of K^+ averaged 77% of total intake resulting in a positive balance of 0.28 g/day (Holbrook et al. 1984). Similar values are reported by Agarwal et al. (1994): ingestion of 90 mmol/day of K^+ in the diet results in absorption of 90% of intake (81 mmol)

and net urinary excretion of a similar amount; thus, normal fecal K^+ excretion average 9 mmol/day. Potassium is primarily absorbed by the duodenum, upon movement of digesta from the stomach to the upper gastrointestinal tract. Duodenojejunal K^+ transport is dependent on the electrochemical potential difference for K^+ between plasma and intestinal lumen and is associated with the osmolarity of digesta, and the absorption of Na^+, water and other nutrients; peak absorption rates are estimated to be 12–15 mmol/h/cm (Agarwal et al. 1994; Lindinger et al. 1999a, b). Absorption of K^+ in the human gastrointestinal tract occurs primarily by passive diffusion via both apical membrane mechanisms and paracellular route into blood via the portal circulation (Agarwal et al. 1994; Hinderling 2016). Feedforward mechanisms arising from gut K^+-sensors result in increased renal K^+ secretion and helps to maintain the plasma $[K^+]$ (Youn 2013; McDonough and Youn 2017). Sustained elevation in plasma $[K^+]$ is also associated with increased rates of intestinal K^+ secretion, thus contributing to fecal K^+ losses (Bia and Defronzo 1981).

Blood

Potassium is present in plasma and blood cells. The plasma $[K^+]$ is around 4 mM at rest in healthy individuals, even in the face of large increases or decreases in K^+ intake (Hinderling 2016). Circadian variation of plasma $[K^+]$ occurs both inter-compartmentally and with renal clearance of K^+ (Moore-Ede et al. 1978). Potassium absorbed from the intestinal tract may result in large elevations in plasma $[K^+]$ (Lindinger et al. 1999a, b), which in turn appears to be sensed by various tissues within the body including vascular smooth muscle, skeletal muscle, pancreas, central nervous system, peripheral nerves and kidneys. In addition to gut sensing of K^+ (Youn 2013), pancreatic insulin secretion is proportional to both the glycemic and kalemic content of meals (Hiatt et al. 1972). Furthermore, erythrocytes in particular have a role in regulating plasma $[K^+]$ during periods of acute increases such as during intense exercise (Lindinger et al. 1999a, b). The associated increases in plasma $[K^+]$, adrenaline, $[H^+]$ and $[lactate^-]$ are able to stimulate a 300-fold increase in the rate of net K^+ uptake by erythrocytes (Lindinger and Grudzien 2003), thus providing an acute but effective means of helping to prevent excessive increases in plasma $[K^+]$.

Renal

Elevated dietary K^+ leads to increased renal K^+ secretion that cannot be fully explained by the elevation of plasma $[K^+]$ (Lee et al. 2007; Lindinger et al. 2000). There is at least one feedforward system between the gut/liver/portal circulation and the kidneys whose primary function appears to proximate a balance between intake and renal excretion (Lee et al. 2007; Youn 2013; McDonough and Youn 2017). Studies in humans have shown that only 20–50% of an acute, oral K^+ load is excreted by the kidneys in < 4 h (Lindinger et al. 2000), therefore, other mechanisms, i.e. extraction by skeletal muscle (Lindinger et al. 1999a, b) and liver (DeFronzo et al. 1980), are evoked to prevent life-threatening hyperkalaemia. Due to the effects of meals and circadian rhythm, the renal excretion of K^+ alternates between net tubular secretion and reabsorption. The active reabsorption of K^+ occurs by active apical Na^+-K^+-$2Cl^-$ cotransporters in the ascending limb of Henle. Tubular secretion of K^+ occurs in the distal convoluted tubule and cortical collecting duct, and is mediated by the apical renal outer medullary K^+ channel and the basolateral NKA (Hinderling 2016). There is net tubular reabsorption of K^+ under normal conditions, perhaps balancing cutaneous losses of K^+ due to passive and active sweating (Hinderling 2016).

Skin

Sweating contributes sizeable losses of K^+ during prolonged exercise or exposure to heat. Ninety minutes of sweating in a cool environment leads to sweat K^+ losses of 4–10 mmol, and an average sweat rate of 1L/h, independently of fluid ingestion (Maughan et al. 2005). Sweat rate and sweat gland K^+ secretion both increase during exercise in hot environments and sweat $[K^+]$ may be as high as 8 mM (Baker and Wolfe 2020). Since the pool of plasma K^+ is low, a total sweat loss of 2L with a mean sweat $[K^+]$ of 6 mM exceeds the plasma K^+ content at rest. The net K^+ loss from cells helps to defend plasma K^+ content during periods of prolonged sweating. Therefore, K^+-containing sports beverages should be considered for endurance-type exercise, especially in hot environments.

Skeletal muscle

Skeletal muscle has an important role in whole-body K^+ balance (Lindinger et al. 1999a, b; McDonough and Youn 2017). It is well-suited for this role (see section below) because of its large mass, i.e. ~ 40% of lean body mass and its ability to 'store' large amounts of K^+, and tolerate increased $[K^+]_i$ to the point determined by the resting E_M and its control of various K^+ channels. Most of the ingested K^+ (up to 80%) is translocated into cells (Bia and Defronzo 1981; Lindinger et al. 1999a, b), with skeletal muscle, liver and kidneys providing front lines of defense for K^+ uptake against potentially life-threatening hyperkalaemia. Elevated plasma insulin stimulates the NKA in skeletal muscle and liver (Clausen and Kohn 1977), to clear K^+ from plasma during and following ingestion of K^+-rich foods (Hinderling 2016). Once extracellular K^+ has been cleared NKA activity

needs to be downregulated to avoid/minimise subsequent hypokalaemia—this is important upon cessation of intense exercise where hypokalaemia can be life-threatening (see below). Factors contributing to the downregulation of muscle NKA activity include decreased $[Na^+]_i$ and increased resting E_M, i.e. voltage-sensitive regulation (Bewick et al. 1999).

Skeletal muscle fibres regulate cellular and tissue K^+ balance

Skeletal muscle fibres regulate the $[K^+]$ on both sides of the sarcolemma. A single transport mechanism such as the NKA, that is only capable of moving K^+ into the cell, is insufficient to regulate cellular K^+ balance (Pirkmajer and Chibalin 2016). Due to the importance of K^+ in determining the resting E_M and how it changes during muscle activity, there are requirements for other means of getting K^+ across the surface and T-system membranes in both directions. Most of the K^+ channels in the surface and T-system

Table 1 Potassium transport proteins expressed in the surface and/or T-system membranes of human skeletal muscle

Protein	Properties	Function	Myopathies
Voltage-sensitive K^+ channels (K_V)			
	Outward rectified		
$K_{Ca}1.1$ (BK)	Sensitive to elevated microdomain $[Ca^{2+}]$. High density in T-system	Delayed then rapid K^+ release during action potential to restore E_M	KCNMA1-linked channelopathy
$K_v1.4$	Fast activation, fast inactivation	May modulate action potential	Andersen-Tawil Syndrome
$K_v3.4$	Fast activation, fast inactivation	May modulate action potential	Implicated in periodic paralysis. Andersen-Tawil Syndrome
$K_v7.5$	Slow activation, slow inactivation	Reduces subthreshold membrane excitability	
Voltage-insensitive K^+ channels			
$K_{Ca}2.2$ (SK2)	Ca^{2+} sensitive open at high $[Ca^{2+}]$	Terminate action potential bursts?	
$K_{Ca}2.3$ (SK3)	Ca^{2+} sensitive open at high $[Ca^{2+}]$	Not present in normal muscle	Present in denervated and myotonic dystrophy
Voltage-insensitive K^+ channels			
	Inward rectified		
$K_{ir}2.1$ (IRK1)	High density in T-system In surface membrane	Membrane stabilisation, K^+ influx, muscle endurance	Periodic paralysis Andersen-Tawil Syndrome
$K_{ir}2.2$	In surface membrane and T-system	E_M stabilisation	Periodic paralysis
$K_{ir}2.6$	At least in surface membrane	E_M stabilisation appears to affect assembly of $K_{ir}2.1$ and K_{ir} 2.2	Periodic paralysis
$K_{ir}6.2$ (K_{ATP})	ATP-sensitive taurine sensitive at least in surface membrane	Link to metabolic state link to NKCC1 protect against catastrophic failure	
Co-transporters			
NKCC1	Na^+, K^+ and Cl^- cotransport	E_M stability at rest and during activity muscle endurance activity may be modulated by $K_{ir}6.2$ Volume regulation during activity	
KCC1	K^+,Cl^- cotransport	Volume regulation muscle endurance	
Na^+/K^+-ATPase (NKA)			
Several isoforms depending on subunit aggregation	Requires locally supplied ATP. Stimulated by catecholamines and insulin	Transports K^+ against electrochemical gradient (into cell)	McArdle's disease

Sources: (Bailey et al. 2019; Cannon 2015; Dassau et al. 2011; DiFranco et al. 2015b; Fialho et al. 2018; Gosmanov et al. 2003; Jurkat-Rott et al. 2006; Kristensen and Juel 2010). Using the nomenclature of (Gutman et al. 2005; Kubo et al. 2005; Wei et al. 2005)

membranes are voltage-gated (termed K_v) which means that they are sensitive to the resting E_M and are either in an open or closed state depending on the type of K^+ channel and resting E_M at that moment. Some of the K_v are termed inward rectifiers, which means that when in an 'open' configuration they permit a flux of K^+ into the cell. Some K_v are outward-rectifiers, thus permitting efflux of K^+. The main types of K^+ transport proteins in skeletal muscle (Table 1), all contribute to membrane excitability, signaling and ion homeostasis. It is important to note that there is considerable variety in K^+ channel terminology—in this review, we have used specific terminology consistent with identified protein structures

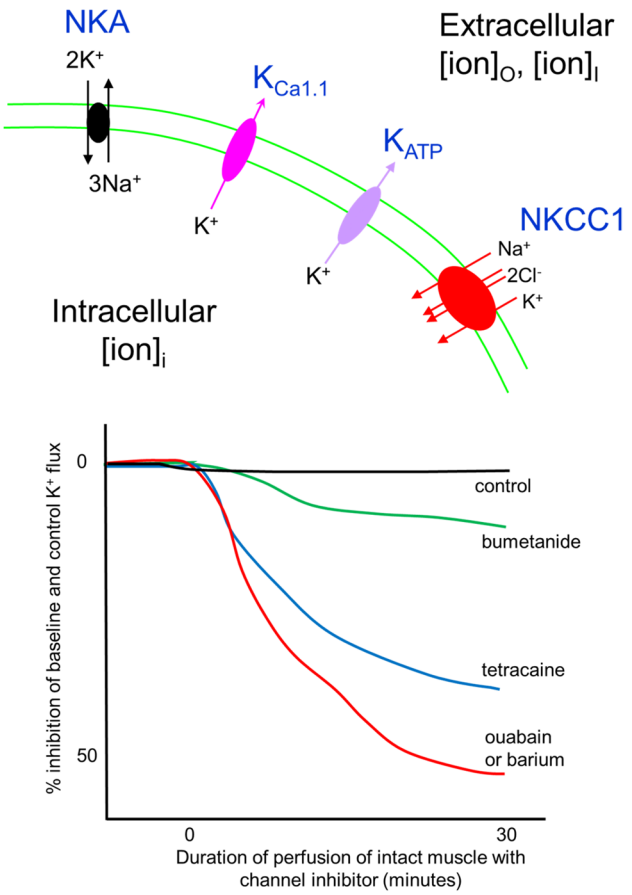

Fig. 2 The main K^+ transport systems in skeletal muscle. Top: Schematic representation of the surface or T-system membrane in a skeletal muscle cell, showing the main types of K^+ transport protein and predominant direction of ion conductance. NKA = sodium–potassium ATPase, $K_{Ca1.1}$ = voltage-gated and calcium-sensitive delayed rectifier K^+ channel, K_{ATP} = ATP-sensitive K^+ channel, NKCC1 = sodium–potassium-2chloride cotransporter, $[ion]_O$ = extracellular ion concentration, $[ion]_I$ = interstitial ion concentration, $[ion]_i$ = intracellular ion concentration. Bottom: Contributions of different K^+ transport systems to K^+ flux into an intact, perfused, mixed muscle system. Bumetanide inhibits NKCC1. Tetracaine inhibits K_{ir} channels. Response to ouabain or barium was nearly identical: ouabain inhibits the NKA; barium is an indiscriminate blocker of all K^+ channels. Figure created using data from Lindinger et al. (2001)

(Gutman et al. 2005; Kubo et al. 2005; Wei et al. 2005) and focus on only the main types identified in skeletal muscle.

The four main types of K^+ transport proteins (Fig. 2, Table 1) function in an integrated manner: (1) to maintain a normal resting E_M when the muscle is quiescent (inward-rectifier K^+ (K_{ir}) channels and NKA); (2) for the repolarisation phase of the action potential (delayed and outward-rectifier K^+ channel (termed $K_{Ca}1.1$); (3) to restore $[K^+]_i$ and $[Na^+]_i$ after the action potential (NKA); (4) to modulate resting E_M during periods of activity (NKA, K_{ir}, NKCC1). The NKCC1 is also involved in the regulation of muscle cell volume during periods of osmotic stress such as occurs at the onset of exercise (Kristensen and Juel 2010; Lindinger et al. 2011). In addition, the K_{ir} 6.2 is an inward-rectifier K^+ channel, sensitive to low micro-domain [ATP], that functions to link metabolic state with resting E_M (Cifelli et al. 2008; Gosmanov et al. 2003). Each transport system is characterised by multiple isoforms depending on fibre-type and genetics (Jurkat-Rott et al. 2006; Kristensen and Juel 2010; Pirkmajer and Chibalin 2016). Structural defects in submits of these proteins results in myopathies (Cannon 2015). Isoforms of many of these channels are also present in the mitochondrial membrane and appear to have roles similar to those in cell surface membranes (Jurkat-Rott et al. 2006; Kristensen and Juel 2010). Skeletal muscle is a complicated tissue, capable of plasticity and adaptation to changes in its environment, responding to chronic changes by changing its phenotype. Characteristics of the phenotype are, in part, determined by the number and types of K^+ transport proteins present which, in turn, are determinants of resting E_M, speed of action potential repolarisation, and fatigability.

Potassium transport proteins

Potassium channels, in addition to Cl^- channels (Nielsen et al. 2017) are important to maintain a stable resting E_M, modulate action potential duration and peak, and restore resting E_M during and after an action potential (Table 1). The predominant outward-rectifier K^+ channel is the "big $K(^+)$" ($K_{Ca}1.1$ or BK) large conductance calcium and delayed voltage-gated K^+ channel. The $K_{Ca}1.1$ channel is more abundant in the T-system than in the sarcolemma (Nielsen et al. 2003a; Tricarico et al. 2005) indicating the important role of the T-system in sequestering released K^+ for rapid re-uptake by NKA at the end of each action potential (Lindinger 2005; Tricarico et al. 2005). The human BK channel structure was determined by Yuan et al. (2010). BK channel activation requires both membrane depolarisation and an increase in intracellular Ca^{2+} to micromolar levels for activation (Yang et al. 2015), therefore, this channel does not operate in normal resting muscle. With muscle activation, high concentrations of Ca^{2+} are attained in local micro-domains through

functional coupling mechanisms with voltage-gated Ca^{2+} channels or channels that release Ca^{2+} from intracellular stores (Fakler and Adelman 2008). The $K_{Ca}1.1$ channel, of which there may be more than one subtype (DiFranco et al. 2012), is responsible for the down-stroke of the action potential that rapidly reestablishes the resting E_M after the rapid Na^+ influx causes the upstroke. $K_{Ca}1.1$ channels, through effects on resting E_M, also function as a critical regulator of muscle contractility during activity (Bailey et al. 2019). During activity, various mechanisms work together to tailor the voltage and Ca^{2+} dependence of channel activation, as well as the kinetics of activation and deactivation gating, for the cell-specific function of BK channels in excitability or K^+ transport (Bailey et al. 2019; Sakamoto and Kurakawa 2019).

The NKA is responsible for creating/maintaining a high $[K^+]_i$, particularly following the rapid efflux through $K_{Ca}1.1$ channels during the action potential and contributes about 50% of the K^+ influx in resting muscle (Fig. 2). The NKA regulates plasma and whole-body $[K^+]$, with NKA activity being influenced by a combination of G-protein mediated increases in intrinsic activity as well as by adaptive modifications to the density of functional NKA units located in surface sarcolemmal and T-system membranes (Pirkmajer and Chibalin 2016). NKA activity is affected by increases in $[K^+]_o$, increases in $[Na^+]_i$, feedforward system from the gastrointestinal tract (related to dietary K^+ load), and circulating hormones including the catecholamines, adrenaline and noradrenaline (anticipatory response to exercise, during all activities and especially intense exercise), insulin (to counteract the effect of Na^+-mediated glucose transport into muscle), amylin and others. The NKA is tetrameric protein comprised of at least three different α-subunits and at least three different β-subunits. The composition depends on the muscle fibre-type, physical training status (Perry et al. 2016) and individual genetics. In muscles of mixed fibre-type at rest, the activity of the NKA contributes 50% to inward flux of K^+ (Fig. 2). With increasing exercise intensity, there is graded increase in NKA activity towards maximal (reviewed by Clausen 2003) that usually prevents $[K^+]_o$ from reaching excessive levels that cause large depolarisations of the membranes of excitable cells. Due to the membrane stabilising effects of Cl^- (Cairns et al. 2004; Clausen 2011; Nielsen et al. 2017), it is now thought that the NKA need not operate at maximal capacity, even with high-intensity exercise. This is consistent with calculations presented in the work of Sejersted and coworkers, as reviewed in Sejersted and Sjøgaard (2000). Based on these data, and on the results of in vitro vastus lateralis muscle NKA activity taken prior to and immediately after the fatigue of high-intensity leg cycling exercise (Hostrup et al. 2014a; Juel et al. 2015), it is evident that moderate to high-intensity exercise can be continued even when in vivo $[K^+]_o$ is substantially elevated.

The adenosine triphosphate (ATP)-dependent K^+ channel (K_{ATP}) appears to be the most abundant K^+ channel present in the sarcolemma (Spruce et al. 1985) and likely exceeds the number of $K_{Ca}1.1$ channels in the T-system (Nielsen et al. 2003a). The K_{ATP} channel is an inward-rectifier channel of the $K_{ir}6.2$ sub-family having SUR1 and SUR1 sulfonylurea receptors. In resting muscle of mixed fibre-type composition in situ, the K_{ATP} channel contributes little to the inward K^+ conductance but does contribute to membrane K^+ leak (Lindinger et al. 2001). When micro-domain [ATP] falls below ~ 1 mM (Spruce et al. 1985), as is likely to occur in some muscle fibres during intense contractions (Söderlund and Hultman 1991), the K_{ATP} channel opening allows for a rapid and selective flux of K^+ across the cell membrane. The sensitivity of the K_{ATP} channel to micro-domain [ATP] indicates a direct link to the metabolic activity of the cell (Zingman et al. 2007). When metabolic activity is high or when blood flow is inadequate cytosolic [ATP] can fall to very low levels (Tupling et al. 2001) in the vicinity of ATP-requiring proteins (NKA, calcium-ATPase). Opening of the K_{ATP} channel under these conditions allows K^+ flux down its electrochemical gradient. This flux is typically outwards (facilitating some membrane polarisation) but may also be into the cell, for example when T-system $[K^+]$ is markedly elevated. In the heart, the K_{ATP} channel is involved in the prevention of catastrophic failure (Ye et al. 2018), and similar role has been proposed for skeletal muscle (Hostrup and Bangsbo 2017). The K_{ATP} channel can be modulated by changes in intracellular concentrations of H^+ and inorganic phosphate, and by phosphorylation such as occurs during periods of intense contractions. Additionally, open K_{ATP} channels function to limit Ca^{2+} influx into fibres during repeated contractile activity (Cifelli et al. 2008).

In general, K_{ir} channels function to stabilise the membrane both at rest and during activity (DiFranco et al. 2015b) and these Ba^{2+}-inhibited channels collectively contribute 40–50% to the K^+ influx in resting, intact muscle of mixed fibre-type (Fig. 2). Rectification refers to the electrophysiological property that the inward K^+ current is larger than the outward K^+ current. This occurs when E_K is more negative than the resting E_M, such as in quiescent muscle and is also likely in the T-system during periods of intense contractions. The K_{ir} conductance is important in establishing and maintaining a relatively stable resting E_M. In contrast to the outward-rectifier voltage-gated K^+ channels (i.e. $K_{Ca}1.1$ and its subtypes) that remain closed at resting E_M, the K_{ir} channels are active, because the resting E_M is depolarised relative to E_K, thus the K_{ir} conductance exerts a stabilising influence on resting E_M through K^+ efflux. The depolarisation during each action potential allows strong rectification to close K_{ir} channels hence abolishing the K_{ir} current during the action potential. Following each action potential, the K_v channels remain closed and K_{ir} becomes active. During

intense muscle activity, the K^+ efflux through $K_{Ca}1.1$ channels likely elevates interstitial and T-system $[K^+]$ (Fraser et al. 2011; Shorten and Soboleva 2007). Under these conditions, the E_K may become depolarised relative to resting E_M which is held negative by the Cl^- gradient (Cairns et al. 2004; Nielsen et al. 2017). A substantial influx of K^+ may occur through K_{ir} channels promoting the clearance of K^+ from the T-system lumen together with NKA mediated K^+ influx (Watanabe and Wada 2020).

The sodium–potassium–chloride cotransporter (NKCC) is the fourth main type of K^+ transport protein in muscle. Only the NKCC1 isoform has been identified in skeletal muscle (Wong et al. 2001) and its activity appears to be linked to micro-domain activation of K_{ATP} (Gosmanov et al. 2003, 2004). The NKCC1 is somewhat active in resting mixed muscle and contributes up to 12% of the inward K^+ conductance (Fig. 2). In resting muscle, the Cl^- current is small since the Cl^- equilibrium potential (E_{Cl}) approaches resting E_M. At rest, under conditions that mimic those in vivo, Cl^- influx via the NKCC keeps the $[Cl^-]_i$ slightly higher than that predicted for passive electrochemical equilibrium, so that E_{Cl} can be about 3 mV depolarised from resting E_M (van Mil et al. 1997). In consequence, there is a 'balancing' efflux of Cl^- through ClC-1 channels that depolarises the sarcolemma. NKCC1 activity is increased with an increase in extracellular tonicity; this may be important for maintenance of cellular volume in inactive skeletal muscle during periods of intense exercise accompanied by increased plasma osmolality (Lindinger et al. 2002, 2011). In contracting muscles, the Cl^- current, primarily through ClC-1 channels with a contribution from NKCC, may contribute to repolarisation during action potentials (de Paoli et al. 2013; Nielsen et al. 2017).

Now that we have introduced the main types and functions of K^+ transport proteins let us examine what happens in human muscles which are of mixed fibre-type composition. This contrasts with the fibre-type predominant muscles of rodents. This is important, because much of what we know has been determined using reductionist in vitro approaches. We, therefore, need to integrate this information with what happens in exercising humans.

K^+ disturbances in plasma, muscle interstitial and intracellular compartments

For many years $[K^+]$ has been measured in the plasma of exercising humans, and sometimes in the muscle intracellular compartment. The $[K^+]_i$ is usually determined from muscle biopsy tissue by calculations using muscle K^+ and fluid contents (Gunnarsson et al. 2013; Kowalchuk et al. 1988; Sjøgaard et al. 1985). Over the last 20 years, the $[K^+]_o$ has routinely been measured in the muscle interstitium ($[K^+]_I$) using the microdialysis technique (Table 2), with a few earlier studies having used K^+-sensitive microelectrodes (Hník and Vyskočil 1981; Vyskočil et al. 1983). Moreover, it has repeatedly been speculated that the $[K^+]$ in the lumen of the T-system of skeletal muscle (with a long tortuous pathway and confined space) exceeds that in the interstitium (Sejersted and Sjøgaard 2000). The T-system $[K^+]$ values have been calculated by modelling and approach 12-14 mM (Fraser et al. 2011; Shorten and Soboleva 2007), although they have yet to be directly measured. These values compare with the higher measured $[K^+]_I$ values during exercise. Moreover, higher $[K^+]_o$ values of up to 50 mM have been calculated for the interfibre space of superfused, isolated rat EDL muscles (Clausen 2011), that markedly exceed the interfibre $[K^+]$ values of 9-10 mM measured with K^+-sensitive microelectrodes (Juel 1986) or microdialysis (Radzyukevich et al. 2009), and hence are questionable. Given this, we focus on measured $[K^+]_I$ values (Table 2).

Plasma K^+ concentrations

The plasma venous $[K^+]$ ($[K^+]_v$) increases rapidly with dynamic exercise as a consequence of K^+ efflux from working muscle fibres as confirmed by an increased arterial-venous $[K^+]$ difference (Green et al. 2000; Kowalchuk et al. 1988; Nielsen et al. 2003b; Vøllestad et al. 1994) in concert with a reduced $[K^+]_i$ (Table 2). This K^+ efflux is thought to occur during each action potential (Clausen et al. 2004; Hník and Vyskočil 1981) mainly via delayed rectifier K^+-channels (DiFranco et al. 2012; Duval and Léoty 1980), and with a contribution via K_{ATP} channels that open later during repeated activation (Pedersen et al. 2009). Furthermore, haemoconcentration contributes to the elevated plasma $[K^+]$ during exercise since fluid moves from plasma to both interstitial and intracellular compartments (Atanasovska et al. 2018; Juel 1988; Lindinger and Heigenhauser 1988; Lindinger et al. 1992). However, the plasma $[K^+]$, when uncorrected for fluid shifts, is the concentration what the heart and many tissue are exposed to. Following exercise cessation, the plasma $[K^+]$ falls rapidly with a half time of ~ 30 s after intense cycling (Vøllestad et al. 1994). Clearly, blood sampled 30-60 s after exercise markedly underestimates peak plasma $[K^+]$ values.

The highest $[K^+]_v$ values recorded in effluent blood of leg muscles in exercising humans is 8-9 mM during treadmill running or cycling (McKenna et al. 1997; Medbø and Sejersted 1990; Vøllestad et al. 1994). When measured in the more remote arm blood vessels the plasma $[K^+]$ is lower than in leg vessels (Table 2) (Saltin et al. 1981). This difference presumably reflects some K^+ uptake by non-working muscle (Lindinger et al. 1990, 1995) and erythrocytes (Lindinger et al. 1992, 1995, 1999) (Fig. 3). During repeated intense exercise, i.e. repeated 30-s sprint bouts,

Table 2 Potassium concentrations in plasma, interstitial and intracellular compartments at rest and with dynamic exercise, static contractions, or ischaemia

	Plasma $[K^+]$ (mM)—arm	Plasma $[K^+]_v$ (mM)—leg	Interstitial $[K^+]$ (mM)	Intracellular $[K^+]$ (mM)	References
Rest	3.9–4.7	3.5–5.4	4.0–4.5	113–165	[1–32]
Dynamic exercise					
Knee extensions		6.0–6.8	9–14	129	[1–7]
Plantar flexions	4.7	5.7	11		[8]
Cycling (high intensity)	4.7–7.0	5.6–8.2	12	110–141	[9–16]
Cycling (repeated)	5.1–6.5	5.4–6.1		105–119	[17–21]
Cycling (prolonged)	4.3–5.4			154–155	[22–25]
Running (high intensity)	6.2	8–9			[26,27]
Running (Yo-Yo test)	5.9, 6.4				[27,28]
Rowing	6.1–7.2				[29–31]
Soccer	4.9				[32]
Static contractions					
(Single or intermittent)	5.4		9–10		[33,34]
Ischaemia					
Skeletal muscle			12–16 (2–3 h)		[35]
Cardiac muscle	4.0		10–12 (5–15 min) 27–31 (50–60 min)		[36–38] [36,37]

Shown are the range of mean values across studies using the largest changes reported for each study. Plasma $[K^+]$ arm or leg refers to measurements in arm or leg blood vessels, respectively. Arm values were from either arterial or venous blood. High-intensity means continuous at, or incremental to, > 100%VO_{2peak}, Repeated means multiple intense bouts of intermittent nature, i.e. 30-s exercise with 4 min rest periods, Prolonged means 50–75%VO_{2peak} continuous with measurements over 44–120 min. Yo-yo test is intermittent shuttle running with increasing intensity. Sources: 1 Juel et al. (1990); 2. Juel et al. (2000); 3. Nielsen et al. (2003a); 4 Nielsen et al. (2003b); 5 Nordsborg et al. (2003); 6. Sjøgaard et al. (1985); 7. Street et al. (2005), 8 Green et al. (2000); 9. Bergström et al. (1971); 10. Gunnarsson et al. (2013); 11. Harmer et al. (2000); 12. Kowalchuk et al. (1988); 13. McKenna et al. (1997); 14. Sahlin et al. (1978); 15. Sjøgaard (1983); 16.Vøllestad et al. (1994); 17. Hargreaves et al. (1998); 18. Lindinger et al. (1990); 19. Lindinger et al. (1992); 20. Lindinger et al. (1995); 21. McKenna et al. (1993); 22. Ahlborg et al. (1967); 23. Costill et al. (1981); 24. Leppik et al. (2004); 25. McKenna et al. (2006); 26. Medbø and Sejersted (1990); 27. Mohr et al. (2011); 28. Krustrup et al. (2006a); 29. Atanasovska et al. (2014); 30. Atanasovska et al. (2018); 31. Nielsen et al. (2002); 32. Krustrup et al. (2006b); 33. Cairns et al. (2017); 34. Vyskočil et al. (1983); 35. Jennische et al. (1982); 36.Watanabe and Gettes (2018); 37 Weiss and Shine (1982); 38. Wilde and Asknes (1995)

the rise in plasma $[K^+]$ diminishes somewhat with consecutive exercise bouts (Hargreaves et al. 1998; Lindinger et al. 1990, 1992, 1995; McKenna et al. 1993). With more prolonged running or cycling at submaximal intensities, e.g. < 75% VO_2peak, there are smaller elevations of plasma $[K^+]$. Even with intense sports such as rowing or soccer the arm measures of plasma $[K^+]$ are not extreme. Notably, physical training has often, but not always, been shown to attenuate or slow the exercise-induced rise of plasma $[K^+]$ (Christiansen 2019; Hostrup and Bangsbo 2017) so that peak plasma $[K^+]$ can be lowered by 0.3–0.5 mM during intense exercise (Harmer et al. 2000; McKenna et al. 1993, 1997). The few studies involving eccentric contractions, which likely incorporate sarcolemmal damage, have not shown the anticipated higher plasma $[K^+]$ values (Goodman et al. 2014; Piitulainen et al. 2008).

Muscle interstitial and intracellular K^+ concentrations

The simultaneous measurement of muscle $[K^+]_I$ and plasma $[K^+]_v$ for working knee extensor or calf muscles reveals gradients of $[K^+]$ between these compartments of up to 6 mM (Green et al. 2000; Gunnarsson et al. 2013; Nielsen et al. 2003b). The average muscle $[K^+]_I$ recorded during intense exercise generally exceed that for plasma $[K^+]_v$ and ranges from 9 to 14 mM (Table 2). The $[K^+]_I$ also shows variability of up to 6 mM between probes inserted into the same working muscle (Juel et al. 2000). It is unknown whether those probes detecting lower $[K^+]_I$ are located adjacent to quiescent fibres (within the working muscle) or adjacent to slow-twitch rather than in fast-twitch fibres given that slow-twitch fibres release less K^+ per action potential than

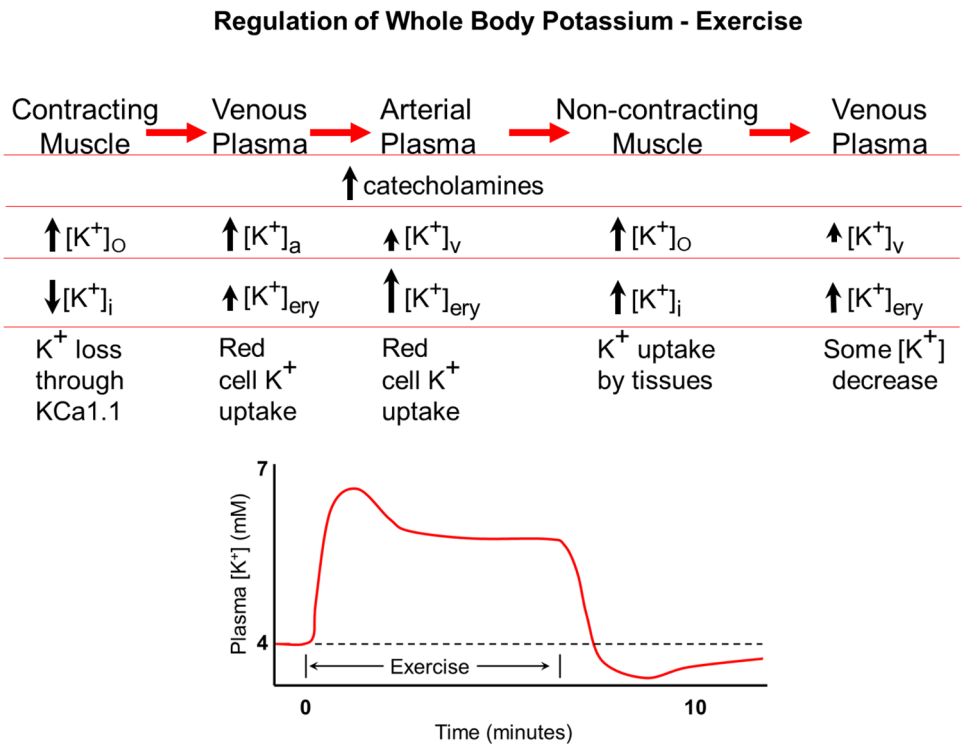

Fig. 3 Schematic overview of regulation of whole-body K^+ balance during exercise. Top: The red arrows indicate the movement of K^+ released from contracting muscle. Changes in tissue $[K^+]$ during moderate to high-intensity exercise indicating regulatory roles of increased catecholamines (activator of NKA), circulating plasma (distribute high $[K^+]$ to whole body), erythrocytes (catecholamine and increased $[K^+]$-mediated reduction of plasma $[K^+]$), other non-contracting tissues (catecholamine and increased $[K^+]$-mediated reduction of plasma $[K^+]$). Bottom: Time course of change in plasma $[K^+]$ reflecting rapid increase at onset of exercise, steady-state phase when net K^+ release from contracting muscles is matched by K^+ extraction by other tissues, and rapid decrease upon cessation of exercise. With high-intensity exercise, plasma $[K^+]$ may remain below baseline for more than 1 h (Lindinger et al. 1992). Figure created using data from (Vøllestad et al. 1994; Lindinger et al. 1999 and Lindinger 1995)

fast-twitch fibres (Clausen et al. 2004). Peak $[K^+]_I$ rises with increasing intensity of dynamic exercise (Juel et al. 2000; Nielsen et al. 2003b; Gunnarsson et al. 2013), or the strength of static contractions (Vyskočil et al. 1983). This indeed is predicted since at more intense workloads there is a higher frequency of action potentials and greater motor unit recruitment. Similarly, $[K^+]_I$ rises progressively with increasing stimulation frequency in animal muscle (Li et al. 2006). Moreover, after physical training the $[K^+]_I$ is lowered by up to 2 mM during intense submaximal exercise (Nielsen et al. 2003b). Interestingly, when a K^+-sensitive microelectrode is abutting the sarcolemma of a single frog muscle fibre the $[K^+]_o$ can increase to 9–10 mM during the K^+-waves associated with each action potential that summate (Hník and Vyskočil 1981). This is suggestive that a higher $[K^+]_I$ exists in an apparent unstirred layer adjacent to a muscle fibre than in the bulk interstitial fluid.

Furthermore, the $[K^+]_i$ falls during exercise from resting values of ~ 160 mM by varying extents but to less than 130 mM with intense exercise (Table 2). The lowest end-exercise $[K^+]_i$ values for human muscle are similar to those in artificially stimulated rodent muscle (Juel 1986, 1988; Lindinger and Heigenhauser 1988). Working skeletal muscle fibres are, therefore, subjected to both raised $[K^+]_I$ along with lowered $[K^+]_i$, whereas quiescent fibres (within contracting or remote muscles) are exposed only to smaller increases of $[K^+]_o$. Remarkably, the $[K^+]_I/[K^+]_i$ value determined for human muscle at the endpoint of exercise (Cairns and Lindinger 2008; Gunnarsson et al. 2013) approaches a similar value measured for stimulated rodent muscle (Juel 1986, 1988; Lindinger and Heigenhauser 1988). Likewise, the calculated resting E_M for exercising human muscle at the end-point (e.g. − 58 mV, Gunnarsson et al. 2013) coincides with the measured E_M values of − 60 to − 55 mV obtained from fatigued rodent muscle (Cifelli et al. 2008; Juel 1986, 1988; Lindinger and Heigenhauser 1988). It appears that there may be a common end-point $[K^+]_I/[K^+]_i$ value (and resting E_M value) with no further rise of $[K^+]_I$ or decline of $[K^+]_i$, regardless of species. This may arise from a lesser activation of the delayed rectifier K^+-channels through a smaller action potential peak (DiFranco et al. 2012) and some

inactivation of these channels (DiFranco et al. 2012; Duval and Léoty 1980).

Ischaemia also has a profound influence on $[K^+]_I$ and resting E_M in both skeletal and cardiac muscle. Prolonged tourniquet ischaemia of rabbit gastrocnemius muscle causes the mean $[K^+]_I$ measured with K^+-sensitive microelectrodes to increase to 12–16 mM over 2–3 h (Jennische et al. 1982). This results in the sarcolemma being depolarised to between − 60 and − 50 mV in mammalian soleus or gastrocnemius muscles (Jennische 1982; Jennische et al. 1982), which rivals the largest depolarisation measured during fatigue. These K^+ disturbances with ischaemia have been attributed to impaired NKA activity (Blum et al. 1988) and possibly K_{ATP} channel opening at very low [ATP] (Tupling et al. 2001). In contrast, the $[K^+]_I$ in the heart increases in a triphasic manner during myocardial ischaemia to markedly exceed that in ischaemic skeletal muscle (Watanabe and Gettes 2018; Weiss and Shine 1982; Wilde and Aksnes 1995). When global ischaemia is imposed on the isolated whole heart, $[K^+]_I$ increases over the initial 5–15 min to a plateau value of 10–14 mM where it remains until climbing slowly to around 30 mM at 50–60 min (Watanabe and Gettes 2018; Weiss and Shine 1982; Wilde and Aksnes 1995). Cardiac contraction is abolished during the initial phase, when $[K^+]_I$ accumulates together with a large acidosis (Watanabe and Gettes 2018; Weiss and Shine 1982). In the third phase, with excessive $[K^+]_I$, the resting force increases and irreversible damage occurs (Weiss and Shine 1982).

Physiological interactive effects with K^+

Several other ionic, hormonal or metabolic changes can accentuate or blunt the effects of raised $[K^+]_o$ on physiological processes. Exercise-induced changes of $[Na^+]$, $[H^+]$, [lactate$^-$], [Cl^-] or Cl^- conductance, and catecholamines can all interact with K^+ disturbances. Rundown of trans-sarcolemmal K^+ and Na^+-gradients act synergistically to reduce skeletal muscle force and M-waves (Cairns and Lindinger 2008; McKenna et al. 2008; Overgaard et al. 1999). An acidosis with lactate$^-$ accumulation appears to convey protection against hyperkalaemic effects in skeletal muscle (de Paoli et al. 2010; Nielsen et al. 2001; Pedersen

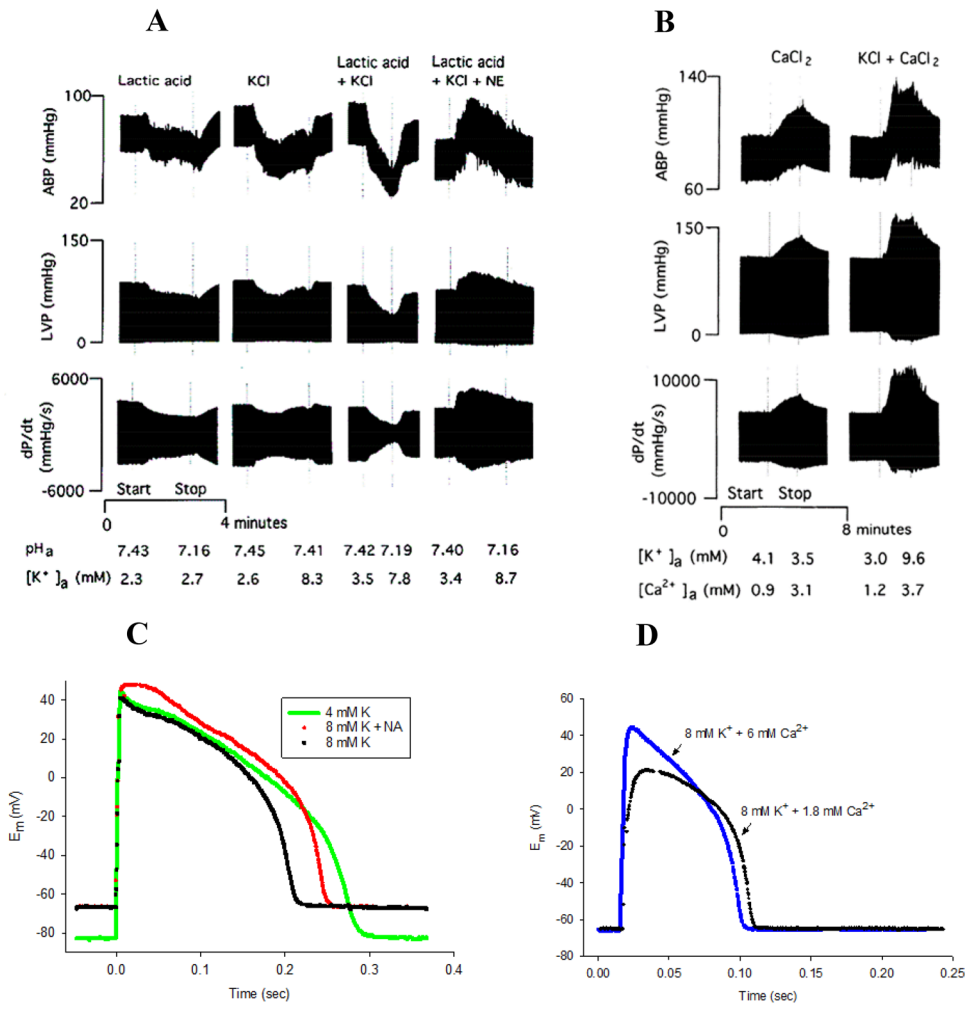

Fig. 4 Influence of raised extracellular $[K^+]$ on cardiac performance and ventricular action potentials: modulation by noradrenaline (norepinephrine) or extracellular calcium. **a** and **b** Cardiac performance in the anaesthetised rabbit in situ at 37 °C is depressed with added KCl and then improved with norepinephrine (NE) or raised extracellular Ca^{2+}. ABP, arterial blood pressure; LVP, left ventricular pressure; dP/dt, rate of left ventricular pressure rise; pHa, arterial pH; $[K^+]_a$, arterial K^+ concentration; $[Ca^{2+}]_a$, arterial Ca^{2+} concentration. **c** and **d** Action potentials in ventricular myocytes from the guinea-pig at 37 °C are depressed with 8 mM K^+ Tyrode solution and restored with noradrenaline (NA) or raised extracellular Ca^{2+}. In C, with added 0.08 µM NA, in D, with 6 mM Ca^{2+}. **a** and **b** figures created using data from (Leitch and Paterson 1994a, b), **c** and **d** from (Paterson et al. 1993)

et al. 2005). In contrast, the combined effects of K^+ with acidosis are extremely detrimental for the heart (Fig. 4a) (Leitch and Paterson 1994a, b). Open ClC-1 channels and a normal trans-sarcolemmal Cl^- gradient initially protect effects of a reduced trans-sarcolemmal K^+ gradient on the resting E_M (and force) in skeletal muscle (Cairns et al. 2004; Clausen 2011; Vaughan-Jones 1982) but not in cardiac muscle (Vaughan-Jones 1982). Whereas later during repeated contractions, a reduced Cl^- conductance becomes protective for skeletal muscle force (Nielsen et al. 2017; Pedersen et al. 2005, 2009). Cardiac sympathetic nerve stimulation can counteract effects of hyperkalaemia on the heart (O'Neill et al. 1993), while circulating catecholamines are protective for K^+-depressed contractions in both cardiac muscle (Fig. 4a, c) (Engstfeld et al. 1961; Leitch and Paterson 1994a) and skeletal muscle (Fig. 5, 7c) (Cairns et al. 1995, 2011; Clausen et al. 1993; Hansen et al. 2005; Uwera et al. 2020). Recent findings suggest that lowered ATP from inhibited glycogenolysis may, via reduced NKA activity, magnify the depressive K^+ effects (Jensen et al. 2020). Hence, multiple physiological changes need to be considered together to fully appreciate the influence of K^+ disturbances on cardiac and skeletal muscle performance in vivo.

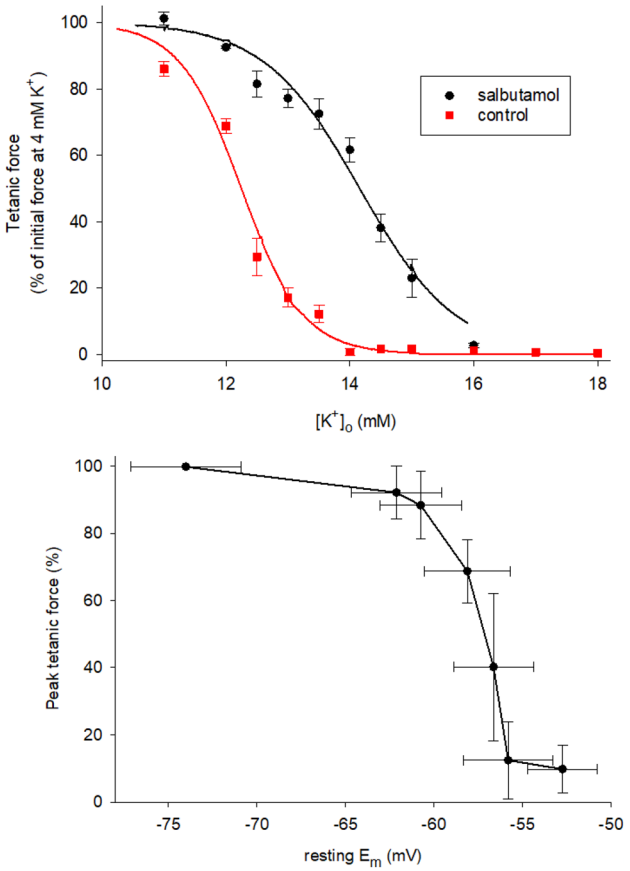

Fig. 5 Raised $[K^+]_o$ causes a depression of peak tetanic force by depolarising the resting E_M in isolated rat skeletal muscle. Top: The peak tetanic force-$[K^+]_o$ relationship in fast-twitch extensor digitorum longus muscle at 30 °C—shifted to the right (towards higher $[K^+]_o$) with added salbutamol (10 µM). Data are mean ± SEM. Bottom: The peak tetanic force-resting E_M relationship determined from $[K^+]_o$ effects on force and resting E_M in slow-twitch soleus muscle at 30 °C. Data are mean ± SD. **a** figures created using data from Hansen et al. (2005), **b** from Cairns et al. (1995)

Integrative effects of K^+ disturbances on body processes

Several physiological processes are known to be influenced by elevated interstitial or systemic K^+ (Table 3) and have been reviewed previously (Clifford and Hellsten 2004; Dempsey et al. 2014; Hník and Vyskočil 1981; Juel 2007; Paterson 1996a, 1997). This section briefly highlights that K^+ exerts multiple effects on different body processes and shows that moderately raised $[K^+]_o$ can support exercise performance.

Muscle blood flow

A number of simultaneous neurogenic and vasodilator mechanisms act to initiate and modulate the skeletal muscle hyperemia that occurs during and following the onset of

Table 3 Multiple physiological effects of raised extracellular $[K^+]$ on body processes

Beneficial effects	Detrimental effects
↑ Muscle blood flow (local hyperaemia)	↑ pain (via afferent feedback)
↑ Exercise pressor reflex (heart rate, ABP)	↑ RPE (via afferent feedback)
↑ Group III/IV afferent feedback	↑ central fatigue (via afferent feedback)
↑ Ventilation (↑ chemosensitivity)	↓ cardiac muscle contractility
↑ Neuromuscular transmission	(arrhythmias, cardiac arrest)
↑ NKA activity	↓ skeletal muscle force/shortening
↑ Skeletal muscle force (twitch potentiation)	(↓ electrical activity, muscle paralysis)

Afferent neural feedback may provide beneficial and/or detrimental effects. Supporting references are throughout the text. Role of K^+ in mediating RPE and central fatigue remains speculative

RPE rating of perceived exertion, *ABP* arterial blood pressure, *NKA* Na^+/K^+-ATPase

exercise (Joyner and Casey 2015). With increased muscle activity, due to the rapid (within seconds) release of K^+ from skeletal muscle fibres, the raised $[K^+]_I$ evokes local vasodilation and an increase in muscle blood flow (Armstrong et al. 2007; Burns et al. 2004; Clifford and Helsten 2004). Potassium infusion experiments promote hyperaemia in resting leg muscle (Juel et al. 2007; Terwoord et al. 2018), through direct effects on vascular smooth muscle (i.e. increased vascular conductance) via inward rectifying K^+ channels (Burns et al. 2004; Juel et al. 2007; Terwoord et al. 2018). Nevertheless, $[K^+]_I$ increases per se make a limited, albeit obligatory, contribution to the total exercise-induced hyperemia (Juel et al. 2007; Terwoord et al. 2018).

Exercise pressor reflex

The notion of a reflex originating in muscle leading to an elevation of heart rate and arterial blood pressure (McCloskey and Mitchell 1972; Saltin et al. 1981) may be instigated by several factors including K^+, H^+, lactate$^-$, phosphate, adenosine, substance P, bradykinin and prostaglandins (MacLean et al. 2000). A role for K^+ is supported by temporal and quantitative associations between increases of heart rate or blood pressure, and increases of either $[K^+]_v$ (Fallentin et al. 1992; Saltin et al. 1981) or $[K^+]_I$ (MacLean et al. 2000). Even small increases of $[K^+]_I$ to just 5 mM can contribute effects (MacLean et al. 2000). However, K^+ infusion experiments that increased plasma $[K^+]$ up to 6.5 mM did not increase heart rate or blood pressure (Juel et al. 2007) which questions the role of K^+ per se in this reflex. Notably, high exercise heart rates cannot be accomplished via this reflex (Dempsey et al. 2014; Paterson 1996a). To mediate the exercise pressor reflex this requires stimulation of muscle afferents (Dempsey et al. 2014).

Afferent feedback

Stimulation of group III–IV muscle afferents occurs with contractions (Caron et al. 2015; Decherchi et al. 1998) or K^+ administration to 5–20 mM $[K^+]_I$ (Caron et al. 2015; Decherchi et al. 1998). Stimulation of this pathway to the central nervous system may, in addition to the exercise pressor reflex, contribute to elevated rating of perceived exertion and central fatigue (with reduced muscle power output) based on pharmacological blockade of these muscle afferents (Amman et al. 2009,2013; Dempsey et al. 2014). Furthermore, temporal associations between elevations of plasma $[K^+]$ and the occurrence of central fatigue during repeated static contractions indicates a possible role for K^+ (Cairns et al. 2017). An elevated $[K^+]_o$ may also evoke the sensation of pain via afferent feedback (Hník and Vyskočil 1981). Pain-indeed manifests with potassium chloride injection when plasma $[K^+]$ exceeds 11 mM (Durelli et al. 1982), yet ischaemic pain can be dissociated from raised $[K^+]_I$ (Green et al. 2000).

Ventilation

The integrated, central regulation of ventilation at rest and during exercise subserves the simultaneous needs to provide oxygen to, and to remove carbon dioxide from, the tissues (Lindinger and Heigenhauser 2012; Keir et al. 2019). This regulation is effected by centrally integrating central and peripheral chemoreceptor, and metaboreceptor responses resulting in multi-level, local control. Potassium is well situated to act as a chemical modulator of ventilation centrally (Linton and Band 1985) and locally, because an increase in its extracellular concentration is a good indicator of increased metabolism. Large increases of plasma $[K^+]$ resulting from ingestion of high K^+-containing beverages can result in elevated ventilation (Lindinger et al. 1999a, b). Raised $[K^+]_I$ may contribute to hyperpnoea during exercise in two ways—by reflex drive from muscle afferents (MacLean et al. 2000; McCloskey and Mitchell 1972), and by sensitising the peripheral chemoreceptors (Linton and Band 1985; Paterson 1997). In support of the first notion, the blocking of the group III–IV afferents, which are normally activated by raised $[K^+]_I$, lowers respiratory rate and ventilation during exercise (Amann et al. 2009; Dempsey et al. 2014). Secondly, a close temporal association exists between plasma $[K^+]_a$ and ventilation in exercising men (Paterson et al. 1989; 1990) which is thought to involve a K^+-induced increase in the chemosensitivity of the carotid body chemoreceptors (Linton and Band 1985; Paterson 1997; Qayyum et al. 1994). This aspect becomes more important with hypoxia (Qayyum et al. 1994) and intense exercise (Paterson et al. 1989) but is only one of many factors underpinning exercise-hyperpnoea (Dempsey et al. 2014; Paterson 1997). These K^+ effects on ventilation are independent of acidosis since it occurs with McArdles syndrome patients whom do not produce H^+ (Paterson et al. 1990).

Neuromuscular transmission

Experimentally raising $[K^+]_o$ to 8–14 mM facilitates both quantal and non-quantal acetylcholine release at the neuromuscular junction in animal models (Ceccarelli et al. 1988; da Silva et al. 2016; Vizi and Vyskočil 1979). Also, K^+ causes an increased frequency of miniature endplate potentials which bolsters the endplate potential amplitude but only when $[Ca^{2+}]_o$ is present (Ceccarelli et al. 1988; Vizi and Vyskocil 1979). Along with this, raised $[K^+]_o$ increases the fusion of synaptic vesicles, (containing acetylcholine), with the presynaptic membrane of the motor-axon terminal (Ceccarelli et al. 1988). Hence, K^+-induced depolarisation of presynaptic membranes augments neuromuscular transmission.

NKA activity

The early work of Skou demonstrated that raised $[K^+]_o$ allosterically activates the NKA (Pirkmajer and Chibalin 2016). However, with the K^+ affinity for the skeletal muscle NKA, i.e. $K_{1/2\ K}$, thought to be ~ 1 mM, it was regarded that the pump was virtually fully activated at the resting $[K^+]_o$ of ~ 4 mM. However, recent findings show that the α_2-isoform of the NKA (present in mammalian T-system membranes) is actually stimulated with up to 10–20 mM $[K^+]_o$ (DiFranco et al. 2015a; Hakimjavadi et al. 2018). Indeed, the outward electrogenic NKA pump current can double between 4 and 10 mM $[K^+]_o$ (DiFranco et al. 2015a) since this current has a $K_{1/2\ K}$, of ~ 4 mM (DiFranco et al. 2015a; Hakimjavadi et al. 2018). This enhanced NKA current and influx of K^+ can provide some resistance to sarcolemmal depolarisation to maintain excitability.

Hypokalaemia and its potential dangers

Both acute hypokalaemia (plasma $[K^+] < 3.5$ mM) and hyperkalaemia (plasma $[K^+] > 5.5$ mM) can aggravate ventricular arrhythmias (Durfey et al. 2017; Trenor et al. 2018), particularly in the absence of the stabilising influence of plasma $[Ca^{2+}]$ (Durfey et al. 2017), catecholamines (Paterson et al. 1993), and for individuals with underlying heath concerns (Durfey et al. 2017; Hoppe et al. 2018). Even in healthy adults without any impairment of K^+ regulation, intense exercise causes elevation of plasma $[K^+]_a$ followed by abrupt hypokalaemia on exercise cessation. Indeed, the post-exercise plasma $[K^+]$ is transiently lower than resting values (Fig. 3) and can reach a nadir of 3.0–3.5 mM at 5–10 min post-exercise (Atanasovska et al. 2014, 2018; Cairns et al. 2017; Gunnarsson et al. 2013; Harmer et al. 2000; Medbø and Sejersted 1990; Vøllestad et al. 1994). The rapid and potentially large fall in plasma $[K^+]$ is consequent to a high NKA activity, resulting in a transient mismatch between K^+ loss and re-uptake by muscles that were previously contracting. This post-exercise hypokalaemia, while typically short-lasting, can pose a threat to stability of the myocardium (Podrid 1990) and possibly contributes to sudden cardiac death (see below).

Hypokalaemia may also be a chronic condition associated with the use of diuretics for treatment of hypertension or chronic heart failure. In these situations, a plasma $[K^+]$ of < 3.5 mM has been associated with a higher risk of atrial fibrillation. Plasma $[K^+]_a < 3$ mM may result in Q-T interval prolongation, Torsade des pointes, ventricular fibrillation, and sudden cardiac death (Collins et al. 2017). In their study of 911,698 men and women with disease and a further 338,297 healthy controls, the prevalence of chronic hypokalaemia amongst individuals aged 55–70 year in the USA was remarkably high. Irrespective of disease, 0.2% of individuals had plasma $[K^+] < 3.0$ mM and nearly 4% of individuals had plasma $[K^+] < 3.5$ mM (Collins et al. 2017). Mortality rates for the hypokalaemic group were 2.5-fold greater than for those with normal plasma $[K^+]$. In this study, there was no association between use of medications, disease state and prevalence of hypokalaemia, indicating that other factors also contribute.

A concern for individuals that have chronic hypokalaemia, whether it is known to them or not, are the effects of a further post-exercise lowering of plasma $[K^+]_a$ on cardiac function. Sudden cardiac death has been reported as a result of intense sexual activities and sporting activities (Asif and Harmon 2017; Hayashi et al. 2015). While hypokalaemia has been implicated because of its potential to cause ventricular tachycardia and fibrillation, it is likely that there is initially an underlying cardiac abnormality that predisposes an individual to death via hypokalaemia (Asif and Harmon 2017; Jazayeri and Emert 2019). The occurrence of hypokalaemia appears to be rare among people participating in endurance events (Mohseni et al. 2011), likely because the submaximal intensity does not necessitate elevated NKA activities and greatly elevated concentrations of circulating catecholamines.

Hypokalaemia, particularly when acute, contributes to direct suppression of K^+ channel conductances in the heart, with recent evidence indicating that indirect effects on activation of Na^+ and Ca^{2+} channels contribute to impaired repolarisation of the cardiac sarcolemma (Weiss et al. 2017). This effect is sufficient to induce early afterdepolarisations and related arrhythmias, including Torsades de pointes, polymorphic ventricular tachycardia and fibrillation. The main effect appears to be a destabilisation of cardiac K_{ir} channels, decreasing the inward and increasing the outward K^+ conductance, despite the hyperpolarisation with lowered $[K^+]_I$ (Weiss et al. 2017). A secondary effect appears to be reduced NKA activity consequent to hyperpolarisation.

Compared to effects on the heart relatively little is known about hypokalaemic effects on skeletal muscle. Studies of resting E_M in rodents generally show a small hyperpolarisation at 1–2 mM $[K^+]_o$, although in some fibres/conditions a depolarisation occurs at < 2 mM $[K^+]_o$ (Akaike 1975; Mølgaard et al. 1980). The peak tetanic force is unchanged at 2 mM $[K^+]_o$ in mouse soleus in vitro (Cairns et al. 2015) but is slightly reduced at 1.2 mM $[K^+]_o$ in mouse EDL (Hayward et al. 2008). Notably, there is a slower fatigue during repeated tetanic contractions in mouse soleus muscles equilibrated at 2 mM $[K^+]_o$ (Cairns et al. 2015).

Hyperkalaemia—function of cardiac and skeletal muscle

Hyperkalaemia is more common than hypokalaemia (Hoppe et al. 2018) and the chronic condition reflects nutrition, renal disease and other health concerns. Acute hyperkalaemia can result from rapid ingestion of K^+-containing foods and beverages, and when coupled with intense exercise can be life-threating with destabilisation of vagal tone, and atrial and ventricular membranes (cardiac dysrhythmia) (Durfey et al. 2017). Raised $[K^+]_I$ and decreased $[K^+]_i$ directly impacts contraction of working skeletal muscle fibres, and elevated plasma $[K^+]_a$ (which raises cardiac $[K^+]_I$) modulates cardiac contractility. When contraction occurs during the course of an ischaemic event the pronounced elevation of $[K^+]_I$ likely impairs skeletal or cardiac muscle function.

It is necessary to preface the next two sections by pointing out that while hyperkalaemia accompanies intense exercise, such high-intensity exercise is typically not otherwise performed by individuals that are experiencing hyperkalaemia of non-exercise origin. Because of the attendant high NKA activities during periods of exercise-induced hyperkalaemia, sustained hyperkalaemia is short-lasting even at high work rates (Vøllestad et al. 1994).

Cardiac muscle

Large elevations of $[K^+]_o$ can induce severe arrhythmias (Durfey et al. 2017), with increases to 20 mM causing cardiac arrest (Ettinger et al. 1974; Jazayeri and Emert 2019; Weiss et al. 2017). But what happens to the heart with smaller elevations of $[K^+]_o$? In the absence of underlying pathologies, the effects of hyperkalaemia on ventricular function include a shortening of the action potential due to altered gating of K^+ channels. Specifically, at 8 mM $[K^+]_o$, the influx of K^+ through K_{ir} channels is increased, even in the face of a reduced driving force for K^+, with decreased K^+ efflux through delayed rectifier K^+ channels. The net effect is an increased repolarising current late in the action potential resulting in a narrowing (Fig. 4c, d) that may compensate against any action potential prolongation and arrhythmia susceptibility (Hegyi et al. 2019). However, such protective mechanisms along with increased circulating catecholamines (Paterson et al. 1993) are not always adequate thus resulting in cardiac arrest or even sudden death (Hegyi et al. 2019).

In anesthetised mammals, the rapid administration of 8–11 mM $[K^+]_o$ diminishes left ventricular pressure, contractile force, and arterial blood pressure (Fig. 4a) (Ettinger et al. 1974; Leitch and Paterson 1994a, b; Logic et al. 1968; O'Neill et al. 1993; Paterson et al. 1992; Surawicz et al. 1967). Dramatic falls in arterial blood pressure and aortic flow only occur at > 11 mM $[K^+]_o$ in vivo (Paterson et al. 1992). At these $[K^+]_o$, there is also a reduced heart rate (Paterson et al. 1992) that may lower the blood pressure. In isolated Langendorff perfused rabbit hearts, rapid increases to 8–12 mM $[K^+]_o$ reduce aortic blood flow and mean output pressure (index of ventricular performance) with such impairments exceeding 50% at 12 mM $[K^+]_o$ (Leitch and Paterson 1994a, b; Paterson et al. 1992; Ryan and Patterson 1996). Cardiac twitch force also becomes depressed at raised $[K^+]_o$ in isolated ventricular or papillary muscle. At 9–10 mM $[K^+]_o$, a 20–30% decrease occurs (Anderson et al. 2004; Robertson and Lumley1989; Ryan and Paterson 1996) followed by complete suppression around 15–18 mM $[K^+]_o$ (Engstfeld et al. 1961).

Studies on intracellular action potentials in ventricular myocytes or muscle strips at 8–2 mM $[K^+]_o$ show depolarisation of resting E_M beyond − 65 mV (Fig. 4c, d) (Kodama et al. 1984; Paterson et al. 1992; Pool-Wilson 1984). The ventricular action potential also displays a smaller overshoot, reduced upstroke velocity, narrower width, and profound slowing of conduction (Fig. 4c, d) (Kodama et al. 1984; Paterson et al. 1992; Pool-Wilson 1984; Wan et al. 2000). Such action potential effects show regional variations in the heart for given increases of $[K^+]_o$ (Wan et al. 2000). All these features can readily be explained by depolarisation-induced inactivation of voltage-gated Na^+ channels and Ca^{2+} channels (Nobel 1979) along with greater inward-rectifier K^+ currents and lesser delayed rectifier K^+ currents (Hegyi et al. 2019). Increases of $[K^+]_o$ to 8 mM lower the stimulation threshold, reflecting an increased sarcolemmal excitability, but 12–16 mM $[K^+]_o$ reduces sarcolemmal excitability (Paterson et al. 1992). Similarly, studies using the electrocardiogram (ECG) show that raised $[K^+]_o$ exerts multiple effects including a decreased or abolished P-wave, widening of the QRS complex with reduced amplitude, ST segment or QT interval depression, and an increased T-wave (Ettinger et al. 1974; Logic et al. 1968; Paterson et al. 1992; Surawicz and Lexington 1967; Weiss et al. 2017).

Raised $[K^+]_o$ (8–12 mM) also exerts direct effects on sinoatrial nodal cells leading to a depolarised maximum diastolic potential, reduced slope of diastolic depolarisation, and decreased amplitude of pacemaker action potentials (Choate et al. 2001). Such $[K^+]_o$ also attenuate the sympathetic drive for sinoatrial nodal pacemaking (Choate et al. 2001). These combined effects lower the heart rate, and predominates at > 10 mM $[K^+]_o$, to oppose the increased heart rate via the exercise pressor reflex which occurs at lower $[K^+]_o$ (MacLean et al. 2000; Saltin et al. 1981).

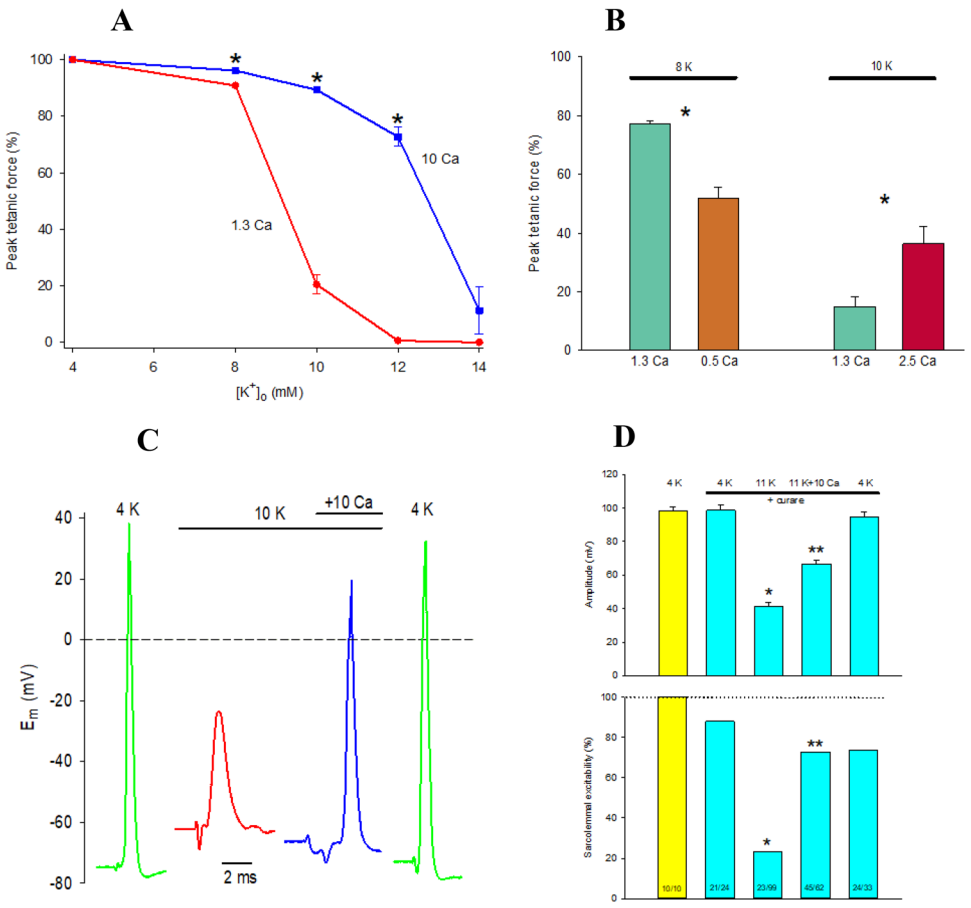

Fig. 6 Influence of raised extracellular $[Ca^{2+}]$ ($[Ca^{2+}]_o$) on K^+-depressed force and action potentials in isolated mouse skeletal muscle at 25 °C. **a** Raised $[Ca^{2+}]_o$ (10 mM) shifts the peak tetanic force-$[K^+]_o$ relationship to the right (towards higher $[K^+]_o$) in soleus muscles. **b** Smaller changes of $[Ca^{2+}]_o$ (1.3–0.5 or 2.5 mM) further depress or partially restore K^+-depressed peak tetanic force (125 Hz) in soleus muscles, respectively. **c** Representative effect of 10 mM $[K^+]_o$ and then 10 mM $[K^+]_o$ plus 10 mM $[Ca^{2+}]_o$ on intracellular action potentials in soleus fibres. Raised $[K^+]_o$ causes depolarisation and a smaller action potential, then added $[Ca^{2+}]_o$ causes a partial repolarisation and larger action potential. **d** Effect of 11 mM $[K^+]_o$ and then 11 mM $[K^+]_o$ plus 10 mM $[Ca^{2+}]_o$ on action potential amplitude and excitability in single extensor digitorum longus fibres. Effects on action potential amplitude are similar to C. Raised $[K^+]_o$ reduces sarcolemmal excitability then is partially restored with raised $[Ca^{2+}]_o$. Data in A,B and D are mean ± SEM. $^*P < 0.05$. Figures created using data from Cairns et al. (2015)

Skeletal muscle

Moderately elevated $[K^+]_o$ (7–10 mM) potentiates twitch and submaximal tetanic contractions in isolated non-fatigued rodent muscle (Cairns et al. 1997, 2011; Pedersen et al. 2019; Yensen et al. 2002). Notably, potassium chloride ingestion that increases plasma $[K^+]$ to 6–7 mM also augments twitches in human muscle (Grob et al. 1957). Such K^+-induced force potentiation does not involve a broader action potential (Yensen et al. 2002) but appears to be mediated via a raised intracellular $[Ca^{2+}]$ ($[Ca^{2+}]_i$) (Pedersen et al. 2019; Quiñonez et al. 2010). Therefore, a moderate hyperkalaemia is likely to enhance muscle contractile performance in vivo.

The peak tetanic force-$[K^+]_o$ relationship has been quantified over 7–15 mM $[K^+]_o$ in isolated whole muscles of animals (Figs. 5 Top, 6a) (Ammar et al. 2015; Broch-Lips et al. 2011; Cairns et al. 1995, 1997; Uwera et al. 2020). Peak force is maintained with smaller increases of $[K^+]_o$ before falling abruptly to complete suppression somewhere between 9 and 14 mM $[K^+]_o$. On the steep part of this relationship a 1 mM $[K^+]_o$ increment or decrement can modulate peak tetanic force by 20–40% initial (Fig. 5 Top). Furthermore, a lowered $[K^+]$ in the solution around a mechanically skinned muscle fibre (mimicking a lowered $[K^+]_i$) that diminishes the K^+ gradient across T-system membranes is sufficient to reduce peak force in single rat fast-twitch fibers (de Paoli et al. 2010; Jensen et al. 2020; Ørtenblad et al. 2003; Watanabe and Wada 2020). Moreover, raised $[K^+]_o$ can reduce power or the extent of muscle/sarcomere shortening (Lucas et al. 2014; Overgaard et al. 2010; Pedersen et al. 2019). Interestingly, a reduced tolerance to raised $[K^+]_o$ occurs

in rat muscles with ageing, i.e. adult versus very young (Pedersen et al. 2005) or by being sedentary versus long-term physically active (Broch-Lips et al. 2011). To mimic the decline of $[K^+]_I/[K^+]_i$ recorded during high-intensity exercise, e.g. from 4.5/125 mM to 11/110 mM (Gunnarsson et al. 2013), an appropriate test $[K^+]_o$ for non-fatigued muscle in vitro, where $[K^+]_i$ does not change (Cairns et al. 2015), would be 12.5 mM, = 11 mM x (125/110), rather than 11 mM. This analytical approach suggests that rundown of the trans-sarcolemmal K^+-gradient of this magnitude would strikingly reduce force (Figs. 5, 6a).

Insightful early work by Vyskocil et al. (1983) furnished the measurements of both force and $[K^+]_I$ during voluntary contractions of human bracioradialis muscle. They found little decline of peak force at 7-8 mM $[K^+]_I$, and then the peak MVC force fell by ~ 30% at 15 mM $[K^+]_I$ (over a 1-min contraction). Thus, larger increases of $[K^+]_I$ can indeed impair contraction of human muscle in vivo, although it is unlikely that this impairment is attributed solely to a K^+ effect since other ionic or metabolic interactions may contribute to, or protect against, this fatigue.

Raised $[K^+]_o$ is well known to depolarise the sarcolemma (Fig. 6c) (Cairns and Lindinger 2008; Sejersted and Sjøgaard 2000) hence, the relationship between peak force and resting E_M, as depicted in Fig. 5 Bottom, is the key to understanding K^+ effects on muscle function (Ammar et al. 2015; Cairns et al. 1995, 1997; Ørtenblad and Stephenson 2003). This relationship shows that there is a large safety margin range for depolarisation of resting E_M before peak force falls markedly over a narrow E_M range, i.e. − 60 to − 55 mV. Hence, force is sensitive to small changes of resting E_M in this range.

K^+-induced depolarisation causes a smaller action potential (Fig. 6c, d; Pedersen et al. 2005; Rich and Pinter 2003; Yensen et al. 2002) and intermittent firing of action potentials during train stimulation (Renaud and Light 1992), which together lowers tetanic $[Ca^{2+}]_i$ (Lucas et al. 2014; Quiñonez et al. 2010). Also, some fibres lose excitability either at rest or during train stimulation (Fig. 6d; Renaud and Light 1992; Rich and Pinter, 2003) and these effects are related to an increased voltage-threshold needed to generate action potentials (Cairns et al. 1997, 2011; Pedersen et al. 2005; Rich and Pinter, 2003). All the K^+-effects can be attributed to inactivation of voltage-gated Na^+ channels in surface and T-system membranes (both slow and fast Na^+ channel inactivation) (Rich and Pinter 2003; Ruff 1996). Notably both Na^+ channel inactivation processes occur at more negative resting E_M in human fast-twitch than slow-twitch fibres (Ruff 1996). In addition, depolarisation may cause inactivation of some T-system voltage-sensor proteins of excitation–contraction coupling (Ferreira-Gregorio et al. 2017; Ørtenblad and Stephenson 2003), although impairment of action potentials is likely to manifest first and hence dominate the force loss (Ørtenblad and Stephenson 2003). Together these processes reduce muscle force or cause paralysis.

Interventions to protect against hyperkalaemia

The acute management of hyperkalaemia has changed little over many years (Grob et al. 1957; Long et al. 2018), despite there now being greater understanding of the mechanisms involved with treatments. The initial aim of acute treatment is to protect the heart from arrhythmias and cardiac arrest, then prevention of skeletal muscle weakness. Clinical treatments involve three approaches: (1) counteracting the sarcolemmal processes in heart/skeletal muscle compromised by K^+-induced depolarisation, (2) lowering plasma or interstitial $[K^+]$ by increased K^+ uptake into cells, and/or (3) attenuating hyperkalaemia by removing K^+ from the body via K^+ binding agents, the kidneys and gut, or dialysis treatment which takes hours. We now discuss the first two approaches for treating hyperkalaemia and compare them with how they influence K^+-induced muscle fatigue.

Calcium

Intravenous injection of a bolus of calcium (as calcium gluconate or calcium chloride) is used to rapidly treat severe hyperkalaemia, i.e. > 6.5 mM plasma $[K^+]$ (Chamberlain 1964; Durfey et al. 2017). Calcium protects via membrane stabilisation (Long et al. 2018) rather than by lowering plasma $[K^+]$ (Bosogno et al. 1994; Chamberlain 1964; Ettinger et al. 1974) with protective effects on the heart appearing within 5 min and lasting for 30–60 min (Chamberlain 1964). In vivo studies show that calcium chloride prevented the K^+-induced depression of ventricular force and aortic flow (Logic et al. 1968). Similarly, raised $[Ca^{2+}]_o$ (1.4–3.0 mM) prevented the decline of left ventricular pressure, dP/dt, and arterial blood pressure, when applied with raised $[K^+]_o$ (Fig. 4b). Moreover, in the isolated perfused rabbit heart increasing $[Ca^{2+}]_o$ stepwise from 1.8 to 10 mM, thwarted the K^+-induced decrease in aortic flow (Leitch and Paterson 1994b). Interestingly, an increase to 5 mM $[Ca^{2+}]_o$ abolished the lowering of heart rate at 12 mM $[K^+]_o$ (Leitch and Paterson 1994b) which likely helped to maintain blood pressure.

Paterson et al. (1993) found that increasing $[Ca^{2+}]_o$ (1.8–6 mM) around K^+-depressed ventricular myocytes restored the action potential amplitude, upstroke velocity, and shortened action potential duration, without reversing the depolarisation (Fig. 4d). Modelling work connects these effects to an increased trans-sarcolemmal Ca^{2+} influx during the action potential to increase $[Ca^{2+}]_i$ (Paterson et al. 1993).

Moreover, raised $[Ca^{2+}]_o$ reverses the adverse ECG changes in hyperkalaemic patients (Chamberlain 1964; Ettinger et al. 1974; Surawicz 1967) or in K^+-depressed isolated perfused hearts (Bisogono et al. 1994). The later effects were mimicked using a Ca^{2+} channel ionophore, but at normal $[Ca^{2+}]_o$. Also, protective effects of raised $[Ca^{2+}]_o$ on the ECG did not manifest when voltage-gated Ca^{2+} channel blockers are present (Bisogono et al. 1994). Hence, Ca^{2+} channels mediate this protective Ca^{2+} effect on the heart during hyperkalaemia.

Potassium-induced weakness in human skeletal muscle is treated with Ca^{2+} infusion (Gamstrop et al. 1957). When $[Ca^{2+}]_o$ is raised (1.3 to 2.5–10 mM) then the peak force of K^+-depressed mouse muscles is partially restored in vitro (Fig. 6a; Cairns et al. 1998, 2015; Hayward et al. 2008; Uwera et al. 2020). This Ca^{2+}-effect occurs via repolarisation of the sarcolemma (up to 5–10 mV) (Albuquerque and Thesleff 1968; Cairns et al. 1998, 2015), which is sufficient to restore force given the steep peak tetanic force-resting E_M relationship (Fig. 5). This repolarisation is intimately linked to raised $[K^+]_i$ possibly due to K^+ influx via the NKCC (Cairns et al. 2015). Such repolarisation promotes a restoration of action potential peak and greater percentage of excitable fibers (Fig. 6c, d) (Cairns et al. 2015; Uwera et al. 2020). Other possible mechanisms for beneficial Ca^{2+} effects on action potentials include a stabilisation of voltage-gated Na^+ channels (Shah et al. 2006) or screening of surface charge (Uwera et al. 2020), but such effects seem unnecessary given the measured repolarisation. Also, a Ca^{2+}-induced recovery of depressed charge movement may occur in depolarised fibres (Ferreira-Gregorio et al. 2017).

Interestingly, studies on animal muscle in vitro have shown that raised $[Ca^{2+}]_o$ (1.3 to 5–10 mM) increases fatigue resistance during stimulation regimes where K^+ shifts are likely to occur. This includes a slower fatigue during repeated tetanic contractions in rodent fast-twitch and slow-twitch muscles (Fig. 7a, b) (Cairns et al. 1998, 2015) or during a prolonged continuous tetanus (Germinario et al. 2008; Rizvi et al. 2019). Comparable studies have not yet been performed on human muscle in vivo.

β-adrenergic agonists

These agents include salbutamol, terbutaline, adrenaline and noradrenaline. When administered by inhalation, nebulisation, or intravenous injection they lower resting plasma $[K^+]$ by 0.4–1.0 mM depending on dose and time (Allon and Copkney 1990; Atanasovska et al. 2018; Hostrup et al. 2014b;

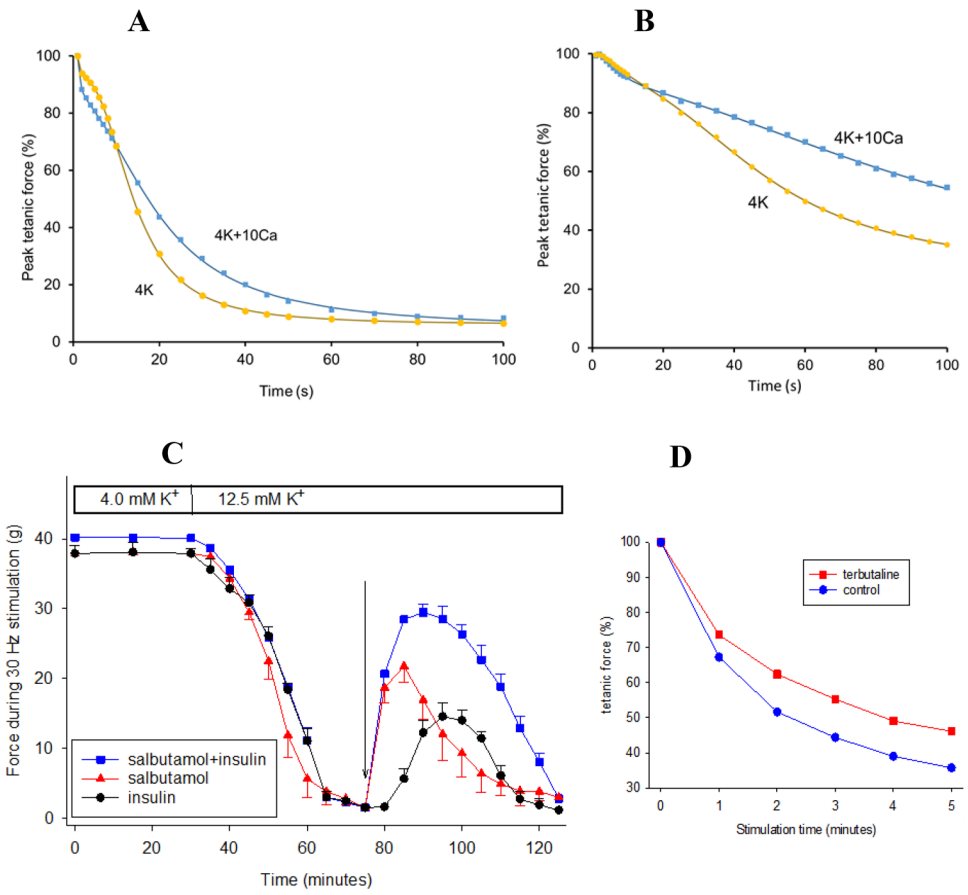

Fig. 7 Interventions that protect against K^+-induced fatigue or K^+-induced paralysis in isolated rodent skeletal muscle. Raised $[Ca^{2+}]_o$ (1.3–10 mM) increases fatigue resistance during repeated tetanic contractions (125 Hz for 500 ms, evoked every 1-s for 100 s) in mice. **a** fast-twitch extensor digitorum longus and **b** slow-twitch soleus muscles. 25 °C. Double-sigmoid functions were fitted to data points in each panel. **c** Salbutamol (10 µM), insulin (100 µUnits/mL), or salbutamol plus insulin (same concentrations), increase peak tetanic force (30 Hz) of rat soleus muscles suppressed with 12.5 mM $[K^+]_o$, 30 °C. Data are mean ± SEM. **d** Terbutaline (10 µM) increases fatigue resistance during repeated tetanic contractions (40 Hz for 300 ms, evoked every 3-s for 5 min) in mouse soleus muscles. **a** and **b** figures created from Cairns et al. (2015), **c** from Clausen et al. (1993), **d** from Juel (1988)

Long et al. 2018) and they prevent the exercise-induced rise of plasma [K^+] (Wang and Clausen 1976). However, the maximum protection occurs in an hour which is much slower than that achieved with Ca^{2+} infusion. This lowering of plasma [K^+] results from K^+ uptake by skeletal muscle and other tissues via stimulation of both NKA (Clausen 2003; Pirkmajer and Chibalin 2016; Wang and Clausen 1976) and NKCC1 activity (Gosmanov et al. 2003; Wong et al. 2001). Such effects are mediated via β_2-adrenergic receptors and increased cyclic adenosine monophosphate (cAMP) levels that increase protein kinase-A activity (Cairns and Borrani 2015). Such myoplasmic changes increase the affinity of NKA to raised $[Na^+]_i$ (Clausen 2003; Pirkmajer and Chibilin 2016) to augment NKA activity (Cairns et al. 1995; Clausen et al. 1993; Juel 1988). Hence, β_2-agonists can lessen hyperkalaemia to improve cardiac and skeletal muscle performance.

With the heart of anesthetised rabbits, exposure to noradrenaline restores left ventricular pressure, dP/dt and arterial blood pressure to counteract the depressive effects of raised $[K^+]_o$, or raised $[K^+]_o$ combined with acidosis (Fig. 4A) (Leitch and Paterson 1994a, b). Similarly, noradrenaline or adrenaline, maintains aortic flow in isolated hearts depressed with 8 or 12 mM $[K^+]_o$ (Leitch and Paterson 1994a, b). Adrenaline also restores force in K^+-depressed papillary muscle from the frog (Engstfeld et al. 1961). Adrenaline or noradrenaline increase the action potential amplitude, upstroke velocity and duration at 8–12 mM $[K^+]_o$ in isolated ventricular myocytes (Fig. 4c) (Paterson et al. 1993). These effects do not involve repolarisation of the sarcolemma even though β-agonists stimulate cardiac NKA activity (Bewick et al. 1999; Desilets and Baumgarten 1986). Instead, it likely involves enhanced trans-sarcolemmal Ca^{2+} influx through voltage-gated Ca^{2+} channels which maintains excitability (Paterson et al. 1993). Indeed, β-agonists increase both cardiac intracellular Ca^{2+}-transients and force via greater Ca^{2+} influx in normal solutions (Kurihara and Konishi 1987). Moreover, some β-adrenergic enhancement of the delayed rectifier K^+ current (Hegyi et al. 2019) may counter impairment of this current by hyperkalaemia.

Salbutamol inhalation attenuates the rise of plasma [K^+] with exercise or potassium chloride ingestion in hyperkalaemic periodic paralysis patients to maintain force in human skeletal muscle in vivo (Wang and Clausen 1976). Indeed, a 1 mM lowering of plasma [K^+] is predicted to convey a considerable protective effect on muscle force at higher $[K^+]_o$ (Fig. 5 Top). Furthermore, β_2-agonists restore force in K^+-depressed rodent skeletal muscle by 10–60% initial in vitro (Figs. 5 Top,7c) (Cairns et al. 1995, 2011; Clausen et al. 1993; Hansen et al. 2005; Uwera et a. 2020) via stimulation of the skeletal muscle NKA (Cairns et al. 1995; Clausen et al. 1993) and likely NKCC activity (Gosmanov et al. 2003; Wong et al. 2001). Such effects are mimicked by the membrane permeable dibutyryl cAMP which supports involvement of cAMP (Clausen 2000). These processes cause a lower interfibre $[K^+]_o$ in isolated human muscle preparations (Ballyani and Grafe 1988) and elevated $[K^+]_i$ (Cairns et al. 1995, 2011; Clausen et al. 1993). Together these effects cause a small but variable repolarisation and a lower $[Na^+]_i$ (Cairns et al. 1995; Clausen et al. 1993; Hansen et al. 2005), which together restores action potential threshold (Cairns et al. 2011) to increase the number of excitable fibres (Uwera et al. 2020), M-wave amplitude/area (Overgaard et al. 1999) and action potential peak (Uwera et al. 2020). If the muscle fibres remain, or become, excitable then β_2-agonists also facilitate action potential mediated Ca^{2+} release from the sarcoplasmic reticulum in animal (Anderson et al. 2012; Cairns and Borrani 2015) and human muscle (Cairns and Borrani 2015; Hostrup et al. 2014a). This effect requires phosphorylation of the ryanodine receptor/Ca^{2+}-release channel of the sarcoplasmic reticulum (Anderson et al. 2012; Cairns and Borrani 2015). However, this mechanism is unlikely to play a major protective role with β_2-agonist treatment for hyperkalaemia in humans since it necessarily requires very high doses (Cairns and Borrani 2015; Hostrup et al. 2014a).

Moreover, high concentrations of β_2-agonist can provide resistance to K^+-induced fatigue during either repeated tetanic contractions in vitro as shown in Fig. 7d (Juel 1988), with similar effects during prolonged tetanic contractions (Cairns and Dulhunty 1994; Rizvi et al. 2018). Human studies have occasionally shown that high β_2-agonist concentrations lower plasma [K^+] and enhance fatigue resistance, i.e. during repeated 30-s sprints (Hostrup et al. 2014b). However, performance improvement is not consistently observed (Altarawneh et al. 2016; Hostrup et al. 2014a) possibly because the β_2-agonists also modulate endogenous catecholamine levels (Hallén et al. 1996).

Insulin

Intravenous injection of insulin (usually as a bolus) lowers plasma [K^+] in humans by 0.6–1.0 mM over an hour (Allon and Copkney 1990; Grob et al. 1957; Long et al. 2018). This effect manifests more rapidly than with β_2-agonists and appears from 15 min (Allon and Copkney 1990). Insulin is usually administered with glucose to prevent hypoglycaemia, although this can still occur as a side-effect (Allon and Copkney 1990; Chothia et al. 2014). Insulin stimulates skeletal muscle K^+ influx by increasing NKA activity, via protein kinase-C and ERK1/2 pathways (Gosmanov et al. 2003; Pirkmajer and Chibalin 2016) leading to phosphorylation of NKA (Chibalin et al. 2001), but does not also stimulate NKCC (Gosmanov et al. 2003; Wong et al. 2001). When insulin and β_2-agonists are added together the fall of plasma [K^+] is amplified to 1.2–1.5 mM which exceeds the effect

of either agent alone (Allon and Copkney 1990). Indeed, there are post-exercise situations when both hormones are elevated in the blood (Marliss and Vranic 2002).

Acute exposure to insulin increases peak force in K^+-depressed skeletal muscle in vitro by stimulating NKA activity (Cairns et al. 1995; Clausen 2000; Clausen et al. 1993), although this effect is weaker than with β_2-agonists (Fig. 7C) (Clausen et al. 1993). The end result is an increased $[K^+]_i$, repolarised E_M, and lowered $[Na^+]_i$, which together restores M-wave amplitude/area to restore peak force by 10–20% (Clausen 2000; Clausen et al. 2003). This insulin effect is additive to that of β-agonists through greater stimulation of NKA activity (Clausen et al. 1993). Despite these well characterised effects, insulin infusion does not also attenuate K^+-induced fatigue during repeated contractions of rat muscle in situ (Karelis et al. 2003).

Glucose

When glucose/dextrose alone is administered either orally or intravenously to normal subjects or patients, it lowers resting plasma $[K^+]$ by 0.4–0.6 mM over 1–2 h (Chothia et al. 2014; Grob et al. 1957) and blunts the rise of plasma $[K^+]$ with an ingested potassium load by 0.3–0.5 mM (Allon et al. 1993). High extracellular glucose per se can phosphorylate the skeletal muscle NKA but in doing so reduces its activity (Chibalin et al. 2001). However, glucose administration triggers endogenous insulin release (Allon et al. 1993; Chothia et al. 2014) but usually to lower levels than with exogenous insulin administration (Chothia et al. 2014). Interestingly, the peptide amylin is co-secreted with insulin from pancreatic β-cells (Pirkmajer and Chibalin 2016). Amylin per se has been shown to stimulate NKA activity and is additive to the effect of insulin to restore force in K^+-depressed skeletal muscle (Clausen 2000). It is tempting to speculate that effects of glucose during hyperkalaemia in vivo may involve amylin. Never-the-less, the lowering of plasma $[K^+]$ with glucose is smaller than for insulin combined with glucose (Chothia et al. 2014; Grob et al. 1957), and yields variable responses. Hence, glucose per se is not recommended as a clinical treatment (Long et al. 2018).

Interestingly, the infusion of glucose, which slightly elevates plasma glucose (5 to 7–10 mM), provides some resistance against fatigue-induced depolarisation (Karalis et al. 2005) and better maintains M-waves and force during fatiguing stimulation of rat skeletal muscle in situ (Karalis et al. 2002,2005). This may encompass acute stimulation of muscle NKA activity (Karalis et al. 2002,2005), which is independent of insulin (Karelis et al. 2003), and possible acts via greater glycolytic ATP supply for the NKA (Karalis et al. 2005). Furthermore, glucose supplementation during prolonged submaximal cycling in humans enhances maximal in vitro NKA activity (Green et al. 2007) and maintains M-waves (Stewart et al. 2007). Alternatively, the elevated glucose may act via increased $lactate^-$ production to improve function of voltage-gated Na^+ channels (Rannou et al. 2012) or to lower sarcolemmal Cl^- channel conductance (de Paoli et al. 2010) both of which restore M-waves and force in K^+ depressed muscle (de Paoli et al. 2010).

Conclusion

K^+ is a univalent cation found in all body fluids, and is important for the normal function of every cell within the body. At rest, whole-body K^+ balance is influenced by dietary K^+ intake, sweating, erythrocyte and skeletal muscle K^+ uptake, and is regulated by the intestinal system and renal clearance in particular. Skeletal muscle fibres can regulate cellular and tissue K^+ balance via four main types of K^+ transport protein—NKA pumps, delayed rectifier K^+ channels, inward-rectifier K^+ channels including K_{ATP} channels, and NKCC1 cotransporters. Contracting skeletal muscle generates an altered K^+ balance not only within itself, but also throughout the entire body. Contracting and quiescent skeletal muscle, other tissues, and cardiac muscle all encounter an altered extracellular K^+ balance during and after intense exercise, with each tissue regulating its $[K^+]_o$, $[K^+]_i$, and resting E_M. Contracting fibres can face exposure to 9–14 mM $[K^+]_I$ during intense exercise with up to 30 mM reductions of $[K^+]_i$. In contrast, quiescent skeletal muscle fibres and cardiac muscle may be exposed to 6–10 mM $[K^+]_o$ during exercise. Post-exercise hypokalaemia, with plasma $[K^+] < 3.5$ mM can be detrimental for the heart, especially in individuals with underlying health concerns.

Moderate elevations of interstitial and plasma $[K^+]$ to 5–9 mM are favorable through stimulating muscle blood flow, the exercise pressor reflex, ventilation, neuromuscular transmission, and muscle NKA activity. Detrimental effects may occur via muscle afferents which mediate pain, perceived exertion and central fatigue. Large elevations of $[K^+]_o$ i.e. > 8 mM, cause severe cardiac arrhythmias, reduce contractile performance and ultimately lead to cardiac arrest. Such effects involve depolarisation and ventricular action potential changes such as a smaller amplitude and narrowing, which are reflected in ECG changes. Similarly, large elevations of $[K^+]_I$ accompanied by lowered $[K^+]_i$ reduce peak tetanic force in fast-twitch and slow-twitch skeletal muscle fibres in association with depolarisation, smaller action potentials and reduced sarcolemmal excitability (intermittent firing of action potentials during trains, or completely inexcitable fibres). The treatments used for severe hyperkalaemia include an initial intravenous injection of Ca^{2+} salt, followed by administration of insulin (with glucose) and sometimes also with β_2-agonist. Mechanisms for treatment interventions involve reducing the hyperkalaemia or protective effects on

the cardiac and skeletal muscle sarcolemma to amend action potentials.

Perspectives

Future studies aimed at increasing our understanding of K^+ regulation should continue to tease apart the surface and T-system membrane contributions in skeletal and cardiac muscle under different (patho) physiological conditions, with consideration for interventions for life-threatening hyperkalaemia and hypokalaemia. An accurate time course of responses of changes in the interstitial concentrations of K^+, Na^+ and Cl^- has yet to be determined in contracting muscle, recovering muscle, and in muscle perfused with altered concentration of these ions. Interstitial methods need to employ rapid time course methods, such as electrophysiology or ion-sensitive dyes, because microdialysis provides poor time resolution. Additional studies need to target the integrated responses of ion transporting systems to address the question of what is the nature of coupling between ion transport systems operating at the microdomain (Sejersted's "fuzzy space") level? Are regulatory responses coordinated amongst control systems, or is each control system responding independently to the substrate/product of its reaction?

Ideally, techniques need to be developed to measure $[K^+]$ simultaneously in multiple compartments (including interstitium, T-system, sub-sarcolemmal space) during various exercise protocols or electrical stimulation regimes, and ultimately in different muscle fibre-types in humans. Hand in hand with $[K^+]$ measurements, it would be extremely valuable to measure resting E_M along with an entourage of other interacting ions (Na^+, Cl^-, Ca^{2+}, H^+, lactate$^-$) that constitute the exercise milieu.

More needs to be understood about K^+ effects on performance of cardiac and skeletal muscle in humans. Hence: (1) determine the peak force-$[K^+]_o$ relationships, and peak force–resting E_M relationships for isolated human skeletal or cardiac muscle cells using close-to-in vivo models; (2) determine the peak force- and peak power-interstitial $[K^+]$ relationships in human muscles during fatiguing exercise in vivo; (3) examine the role(s) of interstitial K^+ in signaling with afferent nerves to understand regulatory feedback that may contribute to elevated perception of exertion and central fatigue.

These types of studies are needed to better understand the coordinated responses of K^+ transport proteins at both the surface and T-system membrane levels in vitro and in vivo. We also need to better understand how altered $[K^+]_o$ and altered resting E_M (by any in vivo physiological means) affects cardiac and skeletal muscle action potentials, which may lead to the development better treatments for hyperkalaemia or to combat K^+-induced exercise fatigue in humans.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

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