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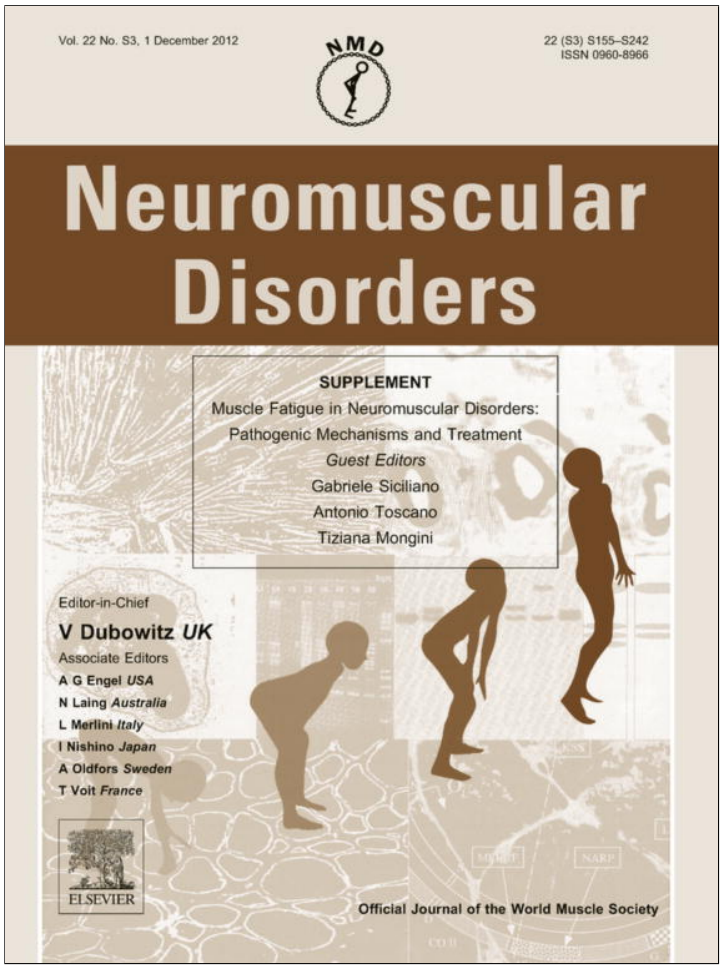

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Membrane excitability and excitation–contraction uncoupling in muscle fatigue

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Abstract

High-frequency tetanic stimulation is associated with an increase in extracellular and T-tubular K^+ and changes of Na^+ and Cl^- concentrations, membrane depolarization as well as inactivation of voltage-gated Na^+ channels. These alterations are expected to lead to fiber inexcitability, which is largely prevented by mechanisms intrinsic or extrinsic to muscle fibers. They act by adapting electrical membrane properties or by accelerating the reconstitution of ionic homeostasis. The high Cl^- conductance of muscle fibers supports the K^+ conductance in fast and complete repolarization and creates a mechanism for the fast reuptake of K^+, thereby reducing the T-tubular K^+ accumulation. Excitability is increased by a Ca^{2+} and proteinkinase C dependent inhibition of the Cl^- conductance which is efficient especially in the T-tubular system. Several mediators activate the Na^+/K^+-ATPase and thus enhance the restoration of ionic homeostasis. Examples are purines (ATP, ADP), calcitonin-gene related peptide and adrenaline. It is also necessary to adapt the strength of the sarcoplasmic Ca^{2+} concentration to the requirements of tetanic contractions. An overwhelming Ca^{2+} signal leads to enzymatically driven excitation–contraction uncoupling. This process is most likely driven by the Ca^{2+} dependent protease μ-calpain and might lead to the long-lasting fatigue observed after excessive physical activity.
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Keywords: Exercise; Cl^- conductance; Extracellular K^+; T-tubular system; Na^+ channels; Na^+–K^+-ATPase; Membrane potential

1. Introduction

The actuation of muscle fiber contraction is a complex process involving several distinct steps. It is initiated by the interplay of various brain regions and propagates over the spinal cord to primary motor neurons, which elicit an action potential at the neuromuscular junction. From there, an action potential wave has to spread along the sarcolemma to excite the complete surface of the muscle fiber. At openings of the transverse tubular system the excitation wave propagates deep into the fiber where electrical excitation is subsequently transduced into contraction by a process called excitation–contraction coupling. This is mainly mediated by Ca^{2+} release from the sarcoplasmic reticulum (SR). At all stages of this complex process, beginning from the motivation to perform limb or body movement, across the initiation and coordination of stimulation of motor neurons, downstream to the muscle fiber itself and its subcellular domains, failure might occur which could be objectively expressed as weakness and might be perceived as fatigue [1]. Activation of a muscle fiber goes along with a sequence of distinct alterations in the physical state of cells followed by their recovery. Repetitive activation, as during exercise, can result in the prolonged persistence of an activated state with incomplete recovery between stimuli. If the rate of stimulation is higher than the rate of recovery, the accumulation of remainders can constitute a striking homeostatic challenge. An accumulation like the tetanic increase of sarcoplasmic Ca^{2+} concentration might be desirable or detrimental, since it increases force but might also trigger excitation–contraction (EC) uncoupling [2].

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Myogenic fatigue ultimately develops if the rate of muscle stimulation is higher than the rate of complete recovery. Homeostatic impairments occur at least on four different levels with different time scales: (i) electrical dis- and recharge of the membrane during the action potential, (ii) changes of Na^+, K^+ and Cl^- concentrations, (iii) Ca^{2+} transients, and (iv) metabolic changes. The action potential represents a rapid discharge of the membrane capacity and its somewhat slower recharge. Since depolarizing currents are mediated by different charge carriers (Na^+) than repolarizing currents (K^+ and Cl^-), every action potential is associated with changes of ion concentrations [3]. The complete restoration of ionic homeostasis is slower than the action potential itself and is not complete within the refractory period. Therefore, fast repetitive stimulation can represent a profound challenge to ionic homeostasis. It compromises excitability and needs mechanisms that upregulate K^+ uptake and Na^+ extrusion or an adaptive reduction of electrical membrane stability in order to avoid excitation failure. On a similar time-scale changes of free Ca^{2+} concentration occur. Ca^{2+} serves as a messenger that activates the contractile machinery but in addition has different signaling functions. The signal Ca^{2+} transmits (initiation of contraction or cell-signaling) depends on its spatial and temporal occurrence. A strong rise of the EC-coupling signal might be overwhelming and disrupt the microdomains of spatially and temporally organized information processing units within muscle fibers [2].

The contribution of reduced excitability to the development of muscle fatigue depends on the type, intensity and duration of exercise. Especially short bouts of high-intense muscle activity might lead to a decline of fiber excitability. More typical modes of exercise are affected by metabolic or other causes of fatigue. In such cases excitability is essentially maintained by several regulatory mechanisms within muscles. The preservation of excitability has to be traded off against the risk of Ca^{2+} overload which disturbs the physiological signaling to the contractile machinery and other Ca^{2+}-dependent signal proteins by the activation of proteases that uncouple the excitation–contraction interface [2]. Here we concentrate on electrical excitation of muscle fibers and excitation–contraction coupling in relation to the development of muscular fatigue during exercise. The paper is based on the comprehensive reviews by Ament et al. [1] and Allen et al. [3]. If not quoted otherwise, statements are reasoned by these reviews.

2. The balance between loss and maintenance of excitability

In respect of electrical excitation, a muscle fiber can be structurally and functionally separated into three distinct compartments: the neuromuscular junction, the sarcolemma and the T-tubular system. Each of these main domains is specialized to serve a distinct function. Their integrated cooperation ensures a reliable and precise electrical response to nerve stimulation. The neuromuscular junction is optimized to elicit a propagating wave of electrical excitation on the sarcolemma with a high safety factor of impulse transmission. It is a highly differentiated structure with membrane infoldings to increase effective surface area and capacitance to provide a large current that excites the adjacent sarcolemma. Dysfunction typically leads to muscle weakness and fatigue in myasthenic syndromes. The sarcolemma longitudinally conducts the action potential wave with high velocity and activates T-tubules at their openings. The T-tubules direct the excitation wave deep into the muscle fiber and are the site where excitation–contraction coupling originates. The access resistance to the T-tubular system unloads the sarcolemmal current source from the very large T-tubular membrane capacitance that represents a big current sink. Thereby it is ensured that the sarcolemma is excited with high conduction velocity, but consequently the T-tubular membrane has to regenerate the action potential by its own equipment of voltage-gated ion channels [4], since pure electrotonic conduction would not be sufficient to activate the EC coupling machinery. Failure of proper excitation of the T-tubular system is typically seen e.g. in myotonia and paramyotonia congenita as well as periodic paralyses [5]. Changes of excitation properties of muscle fibers are quite common during exercise. Stimulation at high frequencies leads to a reduction of muscle fiber excitability at the sarcolemma and the T-tubular membrane which results in a reduction of conduction velocity or even block. In the surface electromyogram the amplitude and area of the muscular compound action potential is smaller and the spectral content is shifted to lower frequencies. It should also be mentioned that, due to the T-tubular access resistance, it is possible that the sarcolemma is well excitable while T-tubules fail [4]. In this case there won't be a reduction of the amplitude or area of the electromyogram.

Excitability can be defined as the amount of current (charge) needed to elicit an action potential, i.e. to reach the threshold for excitation. It is based on voltage- and time dependent properties of voltage-gated Na^+ channels which, during an action potential, transit through a fixed sequence of conformational states (Fig. 1). At resting conditions about half of the channels are in a closed-activatable state. They open when the membrane potential is depolarized above the threshold of excitation, at which depolarizing currents (carried by Na^+) are of the same size as hyperpolarizing currents (carried by Cl^- and K^+). If the membrane is depolarized slightly above this threshold, depolarizing currents become continuously larger than hyperpolarizing currents, because voltage-gated Na^+ channels open in a positive feedback fashion mediated by the depolarizing membrane potential. Time-dependent fast inactivation of voltage-gated Na^+ channels stops the upstroke of the action potential. Repolarization of the membrane potential is mediated by an inward Cl^- flux and outward currents via voltage-gated K^+ channels. Repolarization not only restores the membrane potential to its resting value but also the state of ion channels, e.g. voltage-gated Na^+ and Ca^{2+} channels, which transit back

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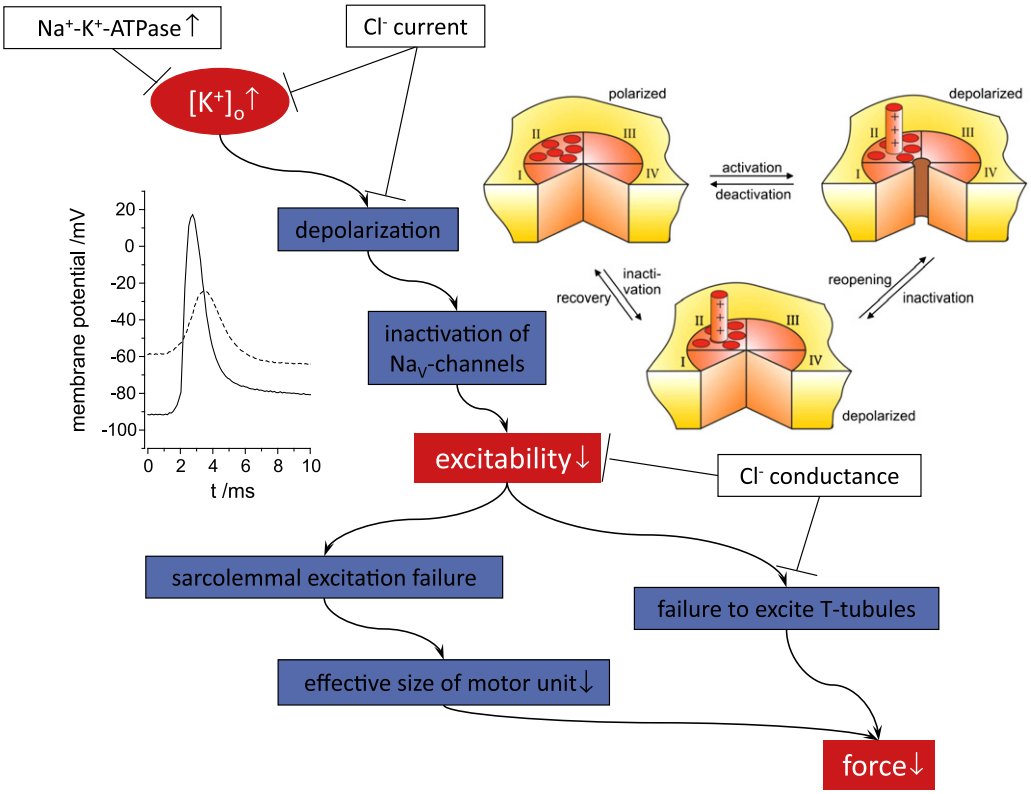

Fig. 1. High-frequency stimulation leads to weakness. Tetanic stimulation results in an increase in extracellular and T-tubular K^+ concentration ($[K^+]_o$) as well as a change of the electrochemical gradient of Na^+ and consequently leads to membrane depolarization. This is followed by closed-state inactivation and incomplete recovery of voltage-gated Na^+ channels (Na_V) which will reduce excitability. State transitions of Na_V channels during an action potential are depicted in a highly schematic manner. The diagram (left panel) shows two action potentials. From a holding potential of −90 mV a regular action potential is triggered (solid line) while from −60 mV only a local non-conducted electrotonic deviation of the membrane potential is provoked (dashed line). Due to sarcolemmal excitation failure the effective size of motor units is reduced. Excitation failure of T-tubules will result in ineffective sarcomere activation. The Cl^--conductance and Na^+–K^+-ATPases are able to delay excitation failure or even maintain excitability. Modified after [5].

from the inactivated to the closed-activatable state, a process that mainly determines the duration of the refractory period. The threshold of excitation is not a static property of a muscle fiber but a dynamically evolving property of every region of the cell membrane. It is determined by the fraction of voltage-gated Na^+ channels that are in the closed-activatable state, by the conductance of Cl^- and K^+ channels that mediate hyperpolarizing currents and thereby stabilize the resting membrane potential and by the strength and frequency spectrum of the stimulating current. The amount of activatable Na^+ channels depends on the membrane potential. Depolarization by only a few millivolts reduces the fraction of activatable channels by a fast and direct transition into a closed-inactivated state and a slow inactivated state. A more pronounced depolarization into the sub-threshold region of membrane potentials (between −60 and −50 mV) is able to drastically impair the excitability of muscle fibers and could even lead to complete inexcitability and conduction block as in various types of periodic paralysis. But at least it causes a relevant prolongation of the refractory period such that the maximal stimulation frequency that can be followed is reduced (Fig. 1). During repetitive stimulation of muscle fibers, as in tetanic activation, there is a continuous decline of the fraction of activatable Na^+ channels due to an incomplete repolarization between action potentials based on changes in ionic homeostasis especially in the T-tubular system and Na^+ channel (slow) inactivation. Changes of ion concentrations are a consequence of high-frequency stimulation since ion fluxes that occur during action potentials are not completely compensated in the short period between action potentials (Fig. 1). The discharge and subsequent recharge of the membrane capacity in the course of an action potential initially results in an exchange of Na^+ for K^+ leading to an increase or decrease of extracellular and T-tubular concentrations of K^+ or Na^+, respectively. The restoration of Na^+ and K^+ distribution relies on the primarily active transport mediated by the Na^+–K^+-ATPase which is a relatively slow process. If the repolarization of the membrane potential had to rely completely on a 1:1 exchange of Na^+ for K^+, changes of ion concentrations occurred very fast and would lead to membrane depolarization already after few action potentials. Especially the T-tubular system which has a very high surface to volume ratio is prone to such changes of ionic homeostasis. In muscle fibers a large part of the repolarization is carried by a Cl^- inward current. Thereby part of the necessary Na^+–K^+ exchange is substituted by Na^+–Cl^- influx [6]. Subsequent changes of Cl^- concentrations result in a much slower change of the resting membrane potential. The

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extracellular and especially T-tubular accumulation of K^+ during activity depolarizes the equilibrium potential of K^+ much faster than the equilibrium potential of Cl^- changes. The high resting Cl^- conductance (up to 8-fold higher than K^+ conductance) pulls the membrane potential close to the Cl^- equilibrium potential. Therefore, it is possible that the membrane potential is hyperpolarized in relation to the K^+ equilibrium potential, thus evoking a K^+ inward current, e.g. via inward rectifying K^+ channels. This mechanism assists in the clearance of K^+ from the T-tubular system. But the ultimate restoration of ionic homeostasis still relies on Na^+–K^+-ATPases. Due to its high resting conductance, the chloride system also has impact on the threshold of excitation. This is of special importance for the T-tubular system, where stimulation occurs with relatively slow kinetics, because the electrical configuration of the T-tubular system in relation to the sarcolemma represents a low-pass filter [4]. High-frequency content of the propagating wave along the sarcolemma ensures the fast sarcolemmal conduction velocity, while the T-tubular system has to be activated primarily by the low-frequency content of the spreading wave.

The equilibrium potential for Cl^- settles down close to the time-averaged membrane potential by passive distribution of Cl^-. Every deviation from the resting membrane potential, e.g. by stimulation induces an opposing current that stabilizes the membrane potential. ClC-1, the predominant Cl^- channel in fibers of skeletal muscle, is an important site for regulation of excitability. During high-frequency stimulation Cl^- conductance is reduced in a first phase and, at least in fast-twitch muscle, later increases upon metabolic exhaustion [4]. The reduction of Cl^- conductance is mediated by a proteinkinase C (PKC) dependent pathway. PKC is activated by Ca^{2+} released from the SR. In addition, a decrease of intracellular pH reduces Cl^- conductance, but during muscle activity the Ca^{2+}–PKC dependent pathway is more sensitive and has a higher gain. This actively regulated decrease of Cl^- conductance serves to maintain membrane excitability particularly in the T-tubular system [4]. It adapts Cl^- conductance to the reduced maximal voltage-gated Na^+ current. SR released Ca^{2+} is a sufficient mediator of this response since a smoother action potential upstroke, a consequence of the reduced Na^+ current, leads to a broadening of the action potential resulting in increased and prolonged sarcoplasmic Ca^{2+} elevations. Metabolic exhaustion results in a strong increase of membrane conductance in rat fast-twitch and probably also slow-twitch muscles [4]. This is due to the opening of ATP-sensitive K^+ channels (K^+ conductance increases about 14-fold) and an increase of Cl^- conductance (about 3-fold) by an unknown mechanism. The high resting conductance is able to block excitation. After cessation of stimulation recovery of initial resting conductance occurs within 1 min. The effect is sensitive to the extracellular glucose concentration. Another study demonstrated that ATP-sensitive K^+ channels (K_{ATP}) play a role in the smoothing of the sarcoplasmic Ca^{2+} concentration during high-frequency stimulation [7]. Blocking of K_{ATP} channels with glibenclamide led to a very strong rise of the Ca^{2+} concentration and muscle force followed by a rapid decline within seconds below control conditions, thus representing increased fatigability. In addition Ca^{2+} concentration did not completely recover between short bouts (200 ms every second) of high-frequency stimulation, resulting in incomplete relaxation. Sarcolemmal and T-tubular membrane excitability is challenged by the aforementioned changes in ion concentrations, mainly the increase of extracellular or T-tubular K^+ concentration. Although the chloride system is able to bridge over a rapid decay of excitability, it is pivotal that ionic homeostasis is restored. This can only be accomplished by the activity of Na^+–K^+-pumps. Hence, despite the intrinsic stimulating action of intracellular Na^+, a variety of auto-, para- and endocrine mediators exist that aim on the activation of Na^+–K^+-ATPases. Active muscle releases purines (ATP, ADP) possibly through pannexin-1 hemichannels [8]. Extracellular ATP stimulates ionotropic (P2X) and metabotropic (P2Y) receptors on the sarcolemma leading to the expression of myokines (IL6) and the stimulation of the Na^+–K^+-ATPase. Changes of Na^+–K^+-ATPase Na^+ affinity and phosphorylation of phospholemman, a Na^+–K^+-pump inhibitor that is repressed if phosphorylated, are mediated by a P2Y-independent pathway [9]. Calcitonin-gene related peptide (CGRP) has been shown to stimulate Na^+–K^+-ATPases in skeletal muscle, but its fatigue-ameliorating effects are mainly mediated by another largely unknown mechanism. Probably it acts by shifting the voltage-dependence of slow inactivation of voltage-gated Na^+ channels [10]. This would increase the number of activatable channels and thereby increase excitability. CGRP is released together with acetylcholine at the neuromuscular junction and has been suggested to be responsible for the walk-through phenomenon seen in patients with hyperkalemic periodic paralysis [11]. Adrenaline is a strong stimulator of Na^+–K^+-ATPases. The effect is mediated by a proteinkinase A dependent pathway via β_2-adrenergic receptors. It is able to improve excitability at high-frequency stimulation. Similar results have been achieved with insulin [3]. These results are derived from in vitro experiments on muscle preparations from rat. Studies employing healthy human volunteers on effects of the β_2-agonist salbutamol on fatigability did not show any significant improvement [12], neither did oral β-blockade has a measurable effect on excitability or myogenic fatigability but slowed the recovery of K^+ homeostasis [13].

3. Excitation–contraction uncoupling in muscle fatigue

The breakdown of ATP during exercise leads to an accumulation of inorganic phosphate (P_i) in the cytoplasm and the release of Mg^{2+} from its complex with ATP [1]. Mg^{2+} is able to counteract the release of Ca^{2+} from the SR. P_i also inhibits Ca^{2+} release by building Ca^{2+}–P_i complexes within the SR and by phosphorylating ryanodine receptors

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(RyRs), the Ca^{2+} release channels of the SR. These mechanisms reduce the Ca^{2+} transient caused by electrical excitation and therefore represent a form of functional EC uncoupling. EC uncoupling in a narrower sense is a phenomenon based on the ultrastructural disruption of the molecular interface between the voltage-sensor L-type Ca^{2+} channel in the T-tubular membrane and the SR Ca^{2+} release channel (RyR) [2]. This complex of proteins is localized to the triad junction and is the molecular correlate of the EC coupling process (Fig. 2). The detailed molecular assembly of the junction is still unknown. Disruption of this interaction results in a strong decrease of Ca^{2+} release and force development upon electrical excitation, since Ca^{2+} influx through L-type Ca^{2+} channels of skeletal muscle is quite low and Ca^{2+} induced Ca^{2+} release too weak to trigger a regular response. EC uncoupling is believed to be responsible for long-lasting fatigue as it occurs after eccentric or excessive muscle activation and the weakness seen in some types of muscular dystrophies and maybe other myopathies [2]. The disruption of the molecular interface between L-type Ca^{2+} channels and RyR is of enzymatic nature. It is likely that it is accomplished by the Ca^{2+}-dependent cysteine protease μ-calpain, an assumption based on the subcellular localization of this protease to the triad junction in uncoupled fibers, various biochemical and pharmacological properties of the uncoupling process and the fact that exogenously applied active μ-calpain causes partial uncoupling of muscle fibers [2]. EC uncoupling is triggered by a strong sarcoplasmic Ca^{2+} load which can be achieved either by an exceptional high Ca^{2+} peak during tetanic contraction lasting for seconds or a prolonged Ca^{2+} signal at a relatively high level. It is interesting in this context that, in the study mentioned in the previous section which investigated the role of K_{ATP} channels in repetitive bouts of fatigue, muscles in which K_{ATP} channels were either inhibited or which stem from a K_{ATP} knock-out mouse showed a delayed and less complete recovery from fatigue [7]. In these muscles sarcoplasmic peak Ca^{2+} concentration was doubled and did not completely decline between tetanic stimulations. It is further interesting that a second bout of fatigue applied at least 30 min after the first seemed to be independent from K_{ATP} channels and showed a similar time-course of cytoplasmic Ca^{2+} and force development as under control conditions during the first bout. The authors called this phenomenon "fatigue pre-conditioning" and differentiated it from ischemic pre-conditioning by showing its independence from adenosine receptor signaling, inhibiting mitochondrial K_{ATP} channels and PKC as well as the use of scavengers of reactive oxygen species. If fatigue pre-conditioning were based on EC uncoupling [14], it would give some functional significance to EC uncoupling in respect to improving muscle performance by shaping the time-course of the cytoplasmic Ca^{2+} signal. In heart muscle it has been suggested that calpain-dependent cleavage of an auto-inhibitory domain in the serine/threonine phosphatase calcineurin leads to the activation of the transcription factor NFAT (nuclear factor of activated T-cells) which triggers a genetic program resulting in myocardial hypertrophy [15]. In skeletal muscle NFAT has been associated with the switch to a slow-twitch fatigue-resistant fiber phenotype [16].

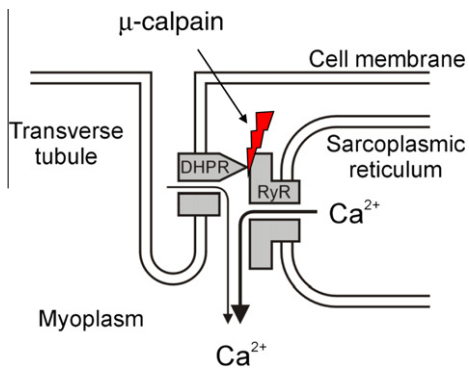

Fig. 2. Mechanism of excitation–contraction (EC) uncoupling. The Ca^{2+}-dependent cysteine protease μ-calpain is believed to disrupt the molecular interaction site between the voltage-sensor of the T-tubular membrane (dihydropyridine receptor, DHPR) and the Ca^{2+}-release channel of the sarcoplasmic reticulum (ryanodine receptor, RyR1). Modified after [5].

4. Concluding remarks

Muscle fatigue evolves due to the slow kinetics of complete recovery from single twitches which is leading to the accumulation of remainders during repetitive stimulation. With regard to sarcolemmal and T-tubular membrane excitability this is expressed by a continuous increment of inactivated voltage-gated Na^+ channels, the extracellular and T-tubular accumulation of K^+ and changes of Na^+ and Cl^- concentrations as well as membrane depolarization. These changes synergistically challenge excitability and are expected, especially at high-frequency stimulation, to contribute to muscle fatigue. In healthy subjects this seems to be avoided by several muscle intrinsic and extrinsic mechanisms that act to maintain excitability. Muscle intrinsic processes involve the high Cl^- conductance which partly relieves the K^+ system from its burden to repolarize especially the T-tubular membrane and that assists Na^+–K^+-ATPases in the clearance of K^+ by hyperpolarizing the membrane potential beyond the equilibrium potential of K^+, thereby reducing the T-tubular and extracellular increase of K^+ concentrations. Activation of PKC by cytoplasmic Ca^{2+} leads to an inhibition of Cl^- channels, thus probably adapting resting membrane conductance to a reduced availability of voltage-gated Na^+ channels and decreased Na^+ current. The Na^+–K^+-ATPase is activated during exercise to accelerate the recovery of ionic homeostasis. This is intrinsically accomplished by an increased intracellular Na^+ concentration but also by auto-, para- and endocrine mediators. Purines like ATP and ADP released from active muscle stimulate Na^+–K^+-ATPases. CGRP is released at the neuromuscular junction together

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with acetylcholine and has been shown to activate Na^+–K^+-ATPases, but probably does also affect the inactivation kinetics of voltage-gated Na^+ channels. Adrenaline is released during exercise. By activating β_2-adrenergic receptors it increases Na^+–K^+-ATPase activity. Although not efficient in healthy individuals, the β_2-agonist salbutamol improves performance in hyperkalemic periodic paralysis and this might also hold for other muscle diseases in which T-tubular K^+ accumulation is a relevant factor for pathogenesis or in which Na^+–K^+-ATPase activity is downregulated, e.g. in various myopathies like muscular dystrophies or McArdle disease. The content of Na^+–K^+-pumps in muscle depends on an individual's activity: training leads to higher while inactivity reduces Na^+–K^+-pump expression. This underscores the importance of training in all kinds of diseases that are linked to reduced physical activity. Among the many changes physical inactivity provokes in the musculature, the decline of its ability to restore K^+ homeostasis is of general importance. In muscular diseases the sequence from sparse physical activity, over muscular remodeling followed by early exhaustion and increased fatigability, leading to insufficient activity could end in a vicious cycle. Despite para- and endocrine mediators other extrinsic factors contribute to the maintenance of excitability during muscle activity. Of special importance might be the "wisdom" of the central nervous system to switch between motor units before fatigue arises and to adapt, i.e. reduce the rate of motor neuron discharge to the prolonged refractory period of muscle fibers – the so called "muscle wisdom" hypothesis. EC uncoupling seems to be an important mechanism for the causation of long-lasting muscle fatigue. It is invoked by overwhelming Ca^{2+} concentrations that probably activate the cysteine protease μ-calpain which is localized to the triad junction and cleaves the molecular bridge between the voltage-sensor and the Ca^{2+} release channel of the excitation–contraction coupling machinery. This procedure might protect muscle fibers from toxic side-effects of prolonged and high cytoplasmic Ca^{2+} concentrations and assist in the proper shaping of the Ca^{2+} signal for optimal tetanic contraction. In addition, it might produce a signal to cell nuclei which induces muscle plasticity by a mechanism similar to what has been proposed for cardiac myocytes.

5. Conflict of interest

None.

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