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In vitro muscle contracture investigations on the malignant hyperthermia like episodes in myotonia congenita

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Background: A common form of congenital myotonia, myotonia congenita (MC), is caused by mutations in the skeletal muscle Cl^- channel gene type 1 (CLCN1). Due to the reduced Cl^- conductance of the mutated channels, the patients may develop generalized muscle rigidity and hypermetabolism during general anaesthesia. The clinical symptoms resemble malignant hyperthermia (MH), which may lead to mistreatment of the patient.
Methods: Muscle specimens of ADR mice (an animal model of MC) as well as of human individuals were used and exposed to potent ryanodine receptor type 1 (RyR1) activators and increasing K^+ concentration. Muscle force was monitored by a standardized diagnostic method for MH, the so-called in vitro contracture test.
Results: Neither muscle of ADR mice nor MC muscle (murine and human myotonic muscle) showed pathological contractures after exposure to the potent RyR1 agonists caffeine and halothane. Increasing concentrations of K^+ had a dose-dependent preventive effect on myotonic stiffness.
Conclusion: We conclude that the adverse anaesthetic MH-like episodes observed in MC patients do not primarily originate from an altered Ca^{2+} release in skeletal muscle. In MC muscle, this hypermetabolism is facilitated by a (pharmacologically induced) sustained depolarization due to an instable membrane potential. The in vitro results suggest that these patients benefit from tight K^+ monitoring because of the membrane potential stabilizing effect of K^+.

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Roughly 50 years after first description, malignant hyperthermia (MH) is still a life-threatening complication of general anaesthesia in genetically predisposed individuals. The pathomechanism is based on excessive Ca^{2+} release via the skeletal muscle Ca^{2+} release channel (ryanodine receptor type 1, RyR1). A clinical crisis is characterized by tachycardia, hypercapnea, metabolic acidosis, hypoxaemia, rhabdomyolysis, and hyperkalaemia with risk of cardiac arrest.[1]

However, there are other conditions that may mimic an MH crisis and do not respond to the specific antidote dantrolene. MH-like reactions during general anaesthesia, and particularly after administration of suxamethonium, have been reported, in particular, in patients with neuromuscular disease.[2]

A common hereditary myopathy is myotonia congenita (MC), which is caused by mutations in the skeletal muscle Cl^- channel gene type 1 (CLCN1) and can be inherited either as an autosomal dominant (Thomsen's myotonia) or autosomal recessive (Becker's myotonia) trait.[3,4] Under normal conditions, influx of Cl^- stabilizes the membrane potential following a depolarization of the muscle fibre membrane. In Thomsen's and Becker's myotonia, however, the reduced Cl^- conductance of the mutated Cl^- channels leads to hyperexcitability of the muscle fibre membrane, leading to bursts of action potentials.[3,5] The clinical picture is characterized by slowed relaxation following forceful voluntary contractions (myotonic stiffness).[4]

Data obtained in the late 1980s suggested a link between MC and MH.[6] However, these data were generated in the pre-molecular era without genetic distinction of the entities. Today, there exist animal models for MC; most often, the so-called ADR mice

(ADR: arrested development of righting response) are used. Hence, we investigate in this study if isolated muscle of ADR mice is susceptible to the classical in vitro triggering agents for MH (i.e. caffeine and halothane). Further, we aim to determine the effects of increasing K^+ levels on the myotonic behaviour (half relaxation time) of isolated myotonic skeletal muscle bundles.

Methods

Muscle dissection and preparation

Animals were kept in the essential specific pathogen-free animal facility of Ulm University. Myotonia was identified in ADR mice clinically by myotonic appearance of the animals (Fig. 1). The homozygous (adr/adr) offspring were distinguished from heterozygous mice (adr/+) by their myotonic phenotype (manifest from day 7 onward), and thus identified as low Cl^- conductance myotonic mice. The adr allele was verified using polymerase chain reaction analysis (for details, see[7,8]). Mice (wildtype and ADR) aging 45–70 days were killed by cervical dislocation after narcosis with CO_2 for at least 2 min, in agreement with the regulations of the local animal welfare committee (Ulm University). The hindlimbs were dissected from the mouse trunk, and after removing the skin they were fixed in a large Petri dish on a thin layer of Sylgard (Dow Corning, Belgium). The mouse's gastrocnemius muscle was dissected and used for the in vitro studies. For attaching the mouse muscle to the force transducer (FT), the femur and tibia were cut with a scissor and used as anchor. The distal end, that is, the Achilles tendon, was fixed with a silk thread.

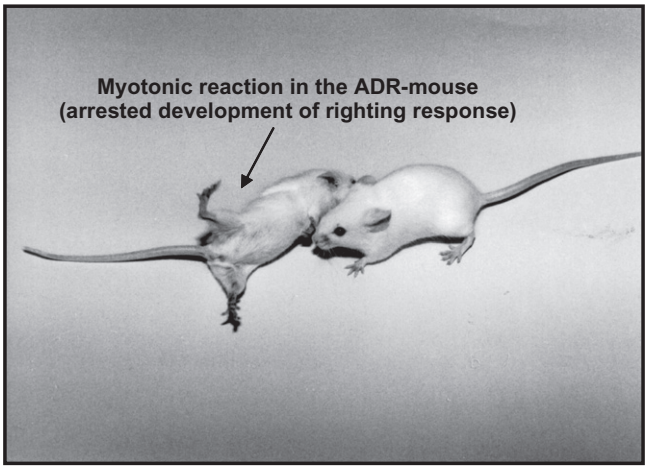

Fig. 1. Myotonic ADR mouse compared with wildtype. The severe muscle stiffness in a myotonic ADR mouse (left) induced by muscle activity compared with a normal control mouse (wildtype, right). Both animals had been laid on back at same time and tried to right themselves. The ADR mouse is smaller than wildtype because of failure to thrive. A similar version of this photograph was previously published by some of our group.[3]

Furthermore, biopsies of vastus lateralis muscle of two patients suffering from MC were used (Table 1). The donors were referred to our neuromuscular centre for muscle biopsy, and specimens were used with informed consent according the local ethics committee.

Myographic registrations

Murine gastrocnemius muscle was mounted in an organ bath and was continuously bubbled with carbogen (95% O_2, 5%CO_2, MTI IndustrieGASE, Neu-Ulm, Germany). For the muscle contraction experiments, physiological Krebs-Ringer solution was used and contained the following (mM): 118 NaCl, 0.8 $MgSO_4$, 1.0 KH_2PO_4, 11.1 glucose, 25 $NaHCO_3$, 2.5 $CaCl_2$. pH was set at 7.4. KCl concentrations were adjusted to 4.5 mM. The temperature was set to 25°C for murine samples and at 37°C for

Table 1

Myotonia congenita patients.
The listed patients underwent the MH-diagnostik IVCT and were tested non-MH suspicious.

Patient 1 – recessive myotonia congenita

The clinical and laboratory findings of Patient 1 were described in detail by some of our group.[27] Briefly, first symptoms were noted at the age of 2, and constantly present during childhood and adolescence. The muscle biopsy was taken with informed consent at our centre at the age of 16. The patient suffered from muscle stiffness especially after rest. With continued muscle activity, for example walking, the myotonic stiffness and following transient weakness disappeared. In the warm-up state, muscle strength was normal in nearly all muscles. Myotonia was not associated with muscle pain. Muscle tissue showed hypertrophy. Creatine kinase levels were in the normal range. Electromyography showed myotonic discharges. Molecular genetics showed a deletion resulting in an early stop codon in the gene of skeletal muscle chloride channel (CLCN1).

Patient 2 – dominant myotonia congenita

Patient 2, a male patient with a history of generalized myotonia, was investigated at the age of 43. The severity of symptoms was constant during childhood, adolescence and adulthood. Typical symptoms included grip myotonia and warm-up phenomenon. Electromyography showed myotonic runs; histopathology showed a lack of type IIb fibres. The patient was shown to carry the chloride channel mutation P480L. This CLCN1 mutation was originally identified in Thomsen's own family.[28]

human samples. A specimen was attached to a highly sensitive FT (Model FT03, Glass Instruments, Quincy, MA, USA). Further, a bridge amplifier and an analog-digital board (Digidata 1200B, Axon Instruments, Union City, CA, USA) were used. Signal recording was performed using a special software (written in Delphi 1.0, Borland International, Scotts Valley, CA, USA), which had previously been developed in our lab.[9] A pair of platinum electrodes was placed on the lateral parts of the muscle for electrical stimulation with supramaximal stimuli (25 V, 1 ms, 0.2 Hz). Mouse gastrocnemius muscle or human vastus lateralis muscle bundles were pre-stretched using optimum force development, roughly 150% of initial length. All experiments started after allowing the muscle to equilibrate in the chamber solution for a period of at least 15 min.

Stock solution (100 mM) of caffeine was added to the tissue bath to yield concentration steps of 1, 2, 3 and 4 mM. Halothane was applied to the tissue baths using a vaporizer (Vapor 19.1 Draeger, Luebeck, Germany) in increasing concentration from 1 to 2, 3, and 4% v/v. The concentration steps were held for 3–6 min. Contracture curves were displayed and recorded with a computer-based data evaluation programme. For further details, see Ording et al.[10]

To investigate the influence of extracellular K^+ concentration on the myotonic activity, K^+ concentrations were varied from 1 to 10 mM in steps of 2 mM in the bath solution. Contraction and relaxation parameters of 20 consecutive muscle twitches were recorded. The muscles and muscle bundles were supramaximally (120%) and repetitively (0.1 Hz) stimulated with electrical pulses of 1 ms duration.

Statistical analysis

All data are presented as mean (standard deviation). The significance of differences between groups was evaluated using Wilcoxon matched pairs signed-rank tests. *P*-values less than 0.05 were considered significant.

Results

Influence of RyR activation on muscle contracture

Myotonic ADR mice were used as an animal model for low Cl^--conductance myotonia (Fig. 1). In a first set of experiments, the effects of Ca^{2+} release from the sarcoplasmic reticulum were investigated by using the potent RyR1 activators caffeine and halothane. Gastrocnemius muscle specimens of ADR and wildtype mice were exposed to these RyR1 agonists in an organ bath. In order to avoid an error originating from myotonic stiffness, all measurements in this set of experiments were conducted after at least 20 min continuous repetitive stimulation of muscle tissue in the so-called 'warm-up' state. Figure 2 shows twitch force and baseline muscle force after challenging the samples with increasing concentrations of the trigger substances. There was a drop of baseline force in the ADR samples, which was not statistically significant. In addition, there was no influence on the relaxation parameters. Importantly, both triggers did not evoke contractures at the used trigger concentrations in the low mM range.

Twitch forces of wildtype muscle exceeded those generated by stimulation of ADR muscle independent of the exposure to RyR1 agonistic drugs. However, myotonic mice were severely handicapped, and the muscles of these animals were somewhat smaller than those of wildtype animals. Furthermore, myotonic muscle is characterized by a fibre-type shift to oxidative type IIa fibres, whereas wildtype muscles contain considerable fractions of type IIb/IIx fibres.

Additionally, the effects of caffeine and halothane were also investigated on muscle specimens obtained from two MC patients (Table 1). Again, there were no pathological contractures in the caffeine/halothane test. The relaxation parameters were not affected.

Influence of K^+ on myotonic activity

Original myographic registrations of increased K^+ levels are shown in Fig. 3. The adr muscle shows a relaxation deficit. A superimposition of single twitches originating from myotonic bursts of action potentials results in a build-up of force resembling the in vitro correlate of myotonic stiffness. Repetitive stimulation leads to a reduction of myotonic stiffness. This phenomenon is known as warm-up. The onset of the warm-up phenomenon and the degree of myotonia is clearly reduced with increasing K^+ concentrations. The also known phenomenon of transient weakness after myotonic activity was not investigated in this study.

Figure 4 shows a systematic evaluation of the effect of K^+ on average relaxation parameters in mouse gastrocnemius muscle from wildtype and ADR muscle. The upstroke of twitches (time to peak) was not influenced by increasing K^+. In contrast, the relaxation deficit was obvious in myotonic muscle as shown by high relaxation times. Increased

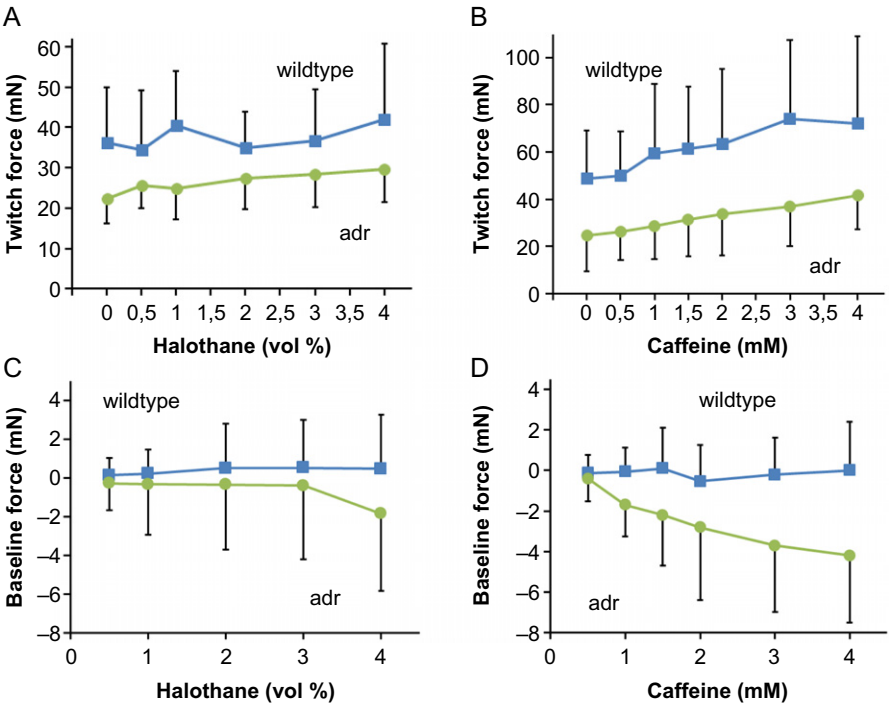

Fig. 2. Myographic force registrations of isolated muscle bundles. The upper panel shows the twitch force after electrical stimulation. (A,B) Both study groups, wildtype (wt, n = 5) and ADR muscle (n = 5) show increasing twitch forces with cumulative doses, indicating a facilitation of myoplasmic Ca^{2+} turnover. The absolute difference in twitch force between wildtype and ADR muscle most likely results from higher cross-sectional area of wildtype muscle compared with smaller ADR gastrocnemius. The change in baseline tension after pharmacological challenge with the classical in vitro triggering substances for malignant hyperthermia (MH) is displayed in the lower panel: (C,D) Contractures of more than 2 mN at 2 % halothane and 2 mM caffeine, respectively, are considered abnormal in the diagnostic in vitro contracture test for MH. Neither wildtype nor ADR muscle shows abnormal contractures to MH triggers (C,D).

K^+ levels caused a concentration-dependent reduction of both measured relaxation parameters (T90/10 and T1/2). The relaxation time reached the control level at 10 mM K^+ in muscle bundles from ADR mice. Compared with physiological K^+ concentrations, twitch forces were significantly lowered at high K^+ in both study groups, wildtype and ADR muscle. In summary, high K^+ acts as antimyotonic.

Discussion

According to literature, the association of MC and MH is controversial.[11–14] There are case reports of patients with MC developing muscle rigidity under inhalational anaesthesia.[15] A case report on a 5-year-old boy with Thomsen's disease, who died after general anaesthesia with a clinical picture resembling an MH episode, suggested an association between MC and MH.[16] Overall, these case reports might well reflect pathological reactions to anaesthetics not linked to true MH, as others have found no association between MC an MH.[14] However, these studies were conducted before molecular genetic testing was available, and therefore might have been mixed up with other myopathies, that is, periodic paralyses or myotonic dystrophy.[14]

Uncontrolled Ca^{2+} release is the key element for the development of an MH crisis. Force generation of muscle specimens (i.e. muscle contracture) serves as a surrogate parameter for myoplasmic Ca^{2+} concentration. This so-called caffeine halothane in vitro contracture test (IVCT) is still the standard method for MH detection.[10] Muscle bundles from MH-susceptible individuals develop abnormal contractures in the IVCT. Our results show clear evidence that neither myotonic muscle from the widely accepted ADR model nor from human MC patients show such abnormal reactions in the IVCT. Thus, these data confirm experiments using myotonic goats (another animal model for MC), wherein the researchers were not able to induce MH with 1% halothane and a single injection of succinylcholine.[12,17]

In conclusion, our results support the notion that MC muscle is not prone to MH events.[14,17] This, however, does not exclude the risk of an MH-like hypermetabolism during general anaesthesia in MC patients. Depolarizing muscle relaxants might cause a severe myotonic episode with life-threatening hyperkalaemia and rhabdomyolysis. Nicotinic acetylcholine receptors (nAChR) are physiologically found at the endplates of skeletal muscle. nAChR are the pharmacological target of succinylcholine and act as unspecific cation channels. In healthy muscle, Cl^- conductance accounts for roughly 70% of the resting membrane potential. In myotonic muscle, the lack of Cl^- conductance leads to an instable muscle membrane potential, which at rest solely

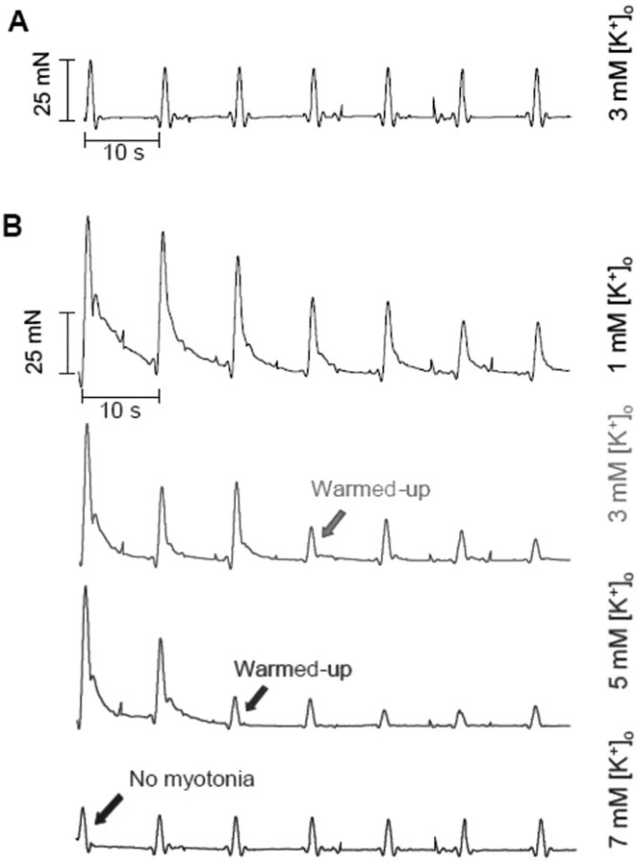

Fig. 3. Original mechanographic registrations showing K^+ *dependence of myotonia. At various* K^+*, the contraction and relaxation parameters kept stable over 20 consecutive twitches. As an example Fig 3A shows an original registration in wildtype muscle at physiological conditions (3 mM* K^+*). Fig 3B shows myotonic stiffness in ADR muscle resembling a quasi-tetanic build-up of force and prolonged relaxation due to after-discharges caused by an instable membrane potential.* K^+ *dose dependently lowers myotonic activity, which can be measured as an earlier onset of the warm-up phenomenon and less serve myotonic muscle reaction.*

depends on K^+ conductance.[3,18] Succinylcholine induces efflux of myoplasmic K^+ and leads to muscle fibre depolarization. Hence, in MC patients, the increased sensitivity to succinylcholine results in myotonic stiffness and consumption of energy carriers. Finally, the activation of the respiratory chain and glycolysis lead to an increase of lactate and acidosis.[2] The clinical distinction of a myotonic episode and MH crisis is obviously difficult. Thus, muscle spasms may be either a result of electrical activity as in myotonia or without electrical activity in muscle contractures due to uncontrolled sarcoplasmatic Ca^{2+} release. Moreover, even myotonic episodes may be associated with increased body temperature.[15,19,20]

The distinction between the two anaesthesia-related complications is of great importance since different underlying mechanisms require different treatments and have different implications for the management of the patient and family.[21] Thus, prompt treatment of MH with dantrolene, a specific blocker of RyR1, resulted in mortality rates of lower than 5%.[22] Based on pathophysiological considerations, treatment of a myotonic crisis should include drugs that produce a use-dependent block of Na^+ channels, and thus reduce hyperexcitability of the membrane, like local anaesthetics and antiarrhythmic drugs of class I (e.g. lidocaine and its derivates).[1,2] If the myotonic crisis is, however, complicated by increased temperature, dantrolene administration might be beneficial because of its depressing effect in all types of muscle-mediated hyperthermia.[2]

In MC patients, depolarizing muscle relaxants and cholinesterase inhibitors have been reported to cause myotonic reactions like masseter spasms or general muscle rigidity, resulting in life-threatening complications in intubation and ventilation.[22] In order to reduce muscle activity, short-acting non-depolarizing muscle relaxants should be used but dosed sparsely to avoid post-operative respiratory failure. The use of propofol was reported to be safe.[21,23–26]

Aside from drugs, myotonic reactions up to paralysis may also be triggered by hypothermia, glucocorticoids, pain and pregnancy. Hence, basic components of anaesthetic management in these patients include keeping patients normothermic, monitoring electrolytes and avoiding hypoglycaemia. In the current study, high K^+ levels caused antimyotonic effects; values above the physiological range, however, resulted in decreased twitch force in myotonic and wildtype animals. Our results suggest that in MC patients, it is favourable to maintain K^+ levels at high normal levels in the perioperative period.

Further information can be found on the websites of the North American (http://www.mhaus.org) and the European MH Group (http://www.emhg.org).

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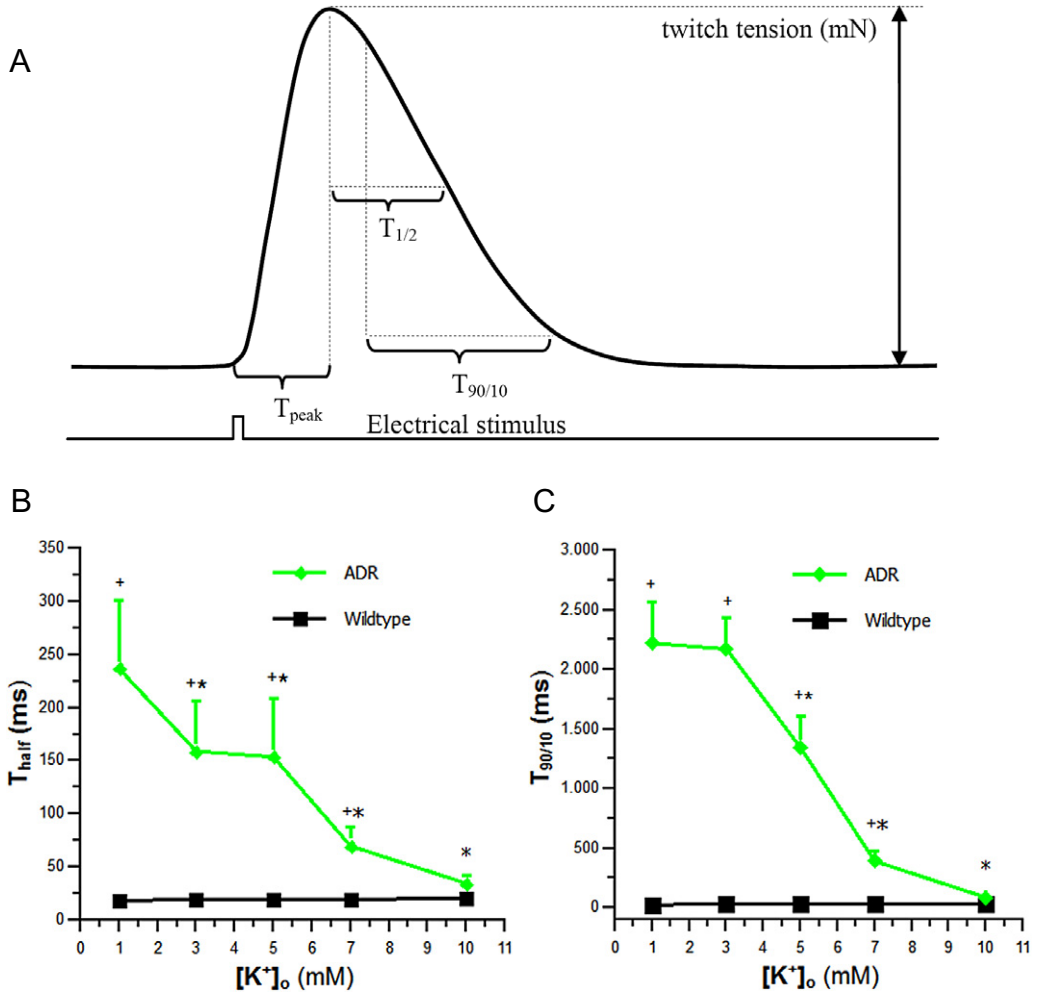

*Fig. 4. Evaluation of myotonic stiffness. Fig 4A shows a sketch of a typical twitch recording with the corresponding parameters used for analysis. The electrical stimulus had a duration of 1 ms and a voltage of 25 V. The parameters that were evaluated were force (mN) – twitch tension, as the maximum force amplitude; Tpeak (ms) – time to peak, measured from the beginning of the pulse until the twitch reached maximum amplitude; T1/2 (ms) – time back to half peak, determined as the time between the peak and the time when the force has decreased to it's half value; and T90/10 (ms) – time from 90% to 10% of peak, determined as the time between 90% of peak and the time when the force has decreased to its 10% value. The relaxation times of ADR muscle and control tissue are displayed in the lower panel (B,C). Influences of extracellular potassium K^+ on the myotonic relaxation deficit measured as Thalf (left) and T90/10 (right). Increasing K^+ dose-dependently lead to a reduction of relaxation times in ADR (n = 12), but not in wildtype (n = 15). High K^+ prevented myotonia. Symbols represent mean values of 20 single twitches (mean ± standard deviation). *Shows significant differences vs. 1 mM K^+; +shows significant differences vs. wildtype.*

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