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ENS TEACHING REVIEW

Skeletal muscle channelopathies

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Abstract Ion channelopathies have common clinical features, recurrent patterns of mutations, and almost predictable mechanisms of pathogenesis. In skeletal muscle, disorders are associated with mutations in voltage-gated Na^+, K^+, Ca^{2+}, and Cl^- channels leading to hypoexcitability, causing periodic paralysis and to hyperexcitabilty, resulting in myotonia or susceptibility to malignant hyperthermia.

Key words ionchannels · hereditary diseases · sodium · potassium · calcium chloride

Introduction

Membrane excitability which is critical for muscle function, is regulated by voltage gated ion channels. It is therefore not surprising, that ion channels are involved in the pathogenesis of diseases of skeletal muscle. Pioneer work on excised muscle tissue of patients with hereditary episodic weakness demonstrated the underlying defect to be a persistent Na^+ inward current depolarizing the membrane and causing inexcitability and weakness [36]. Cloning and analysis of the gene encoding the voltage gated Na^+ channel of skeletal muscle revealed the first mutations associated with impaired ion channel function and confirmed hyperkalemic periodic paralysis to be a Na^+ channel disorder [18]. Since then, over twenty diseases now termed as channelopathies, have been described [for review see 40]. Best understood are the disorders of skeletal muscle which serve as a paradigm for episodic disorders of brain and heart such as migraine, epilepsy, and cardiac arrhythmia.

Muscle physiology

Motoneuron activity is transferred to skeletal muscle in the neuromuscular junction generating an action potential in the muscle that propagates along the surface membrane including the transverse tubular system (TTS), a membrane region projecting deep into the cell to ensure even distribution of the impulse. The upstroke of the action potential is mediated by opening of the voltage gated Na^+ channels (encoded by the *SCN4A* gene and its accessory beta-subunit encoded by *SCN1B*) that elicit a Na^+ inward current with rapid activation kinetics. Repolarization of the membrane by rapid Na^+ channel inactivation is additionally supported by opening of K^+ channels (encoded by *KCNC4* and its accessory subunit encoded by KCNE3) that mediate an outward K^+ current. Buffering of after potentials is achieved by a high Cl^- conductance near the resting potential resulting from the homodimeric Cl^- channel encoded by *CLCN1*.

At specialized junctions in the TTS, the signal is transmitted from the outer membrane to the inside causing the release of Ca^{2+}-ions from the sarcoplasmic reticulum (SR) which in turn activates the contractile apparatus, a process called excitation-contraction coupling. Mainly two Ca^{2+} channel complexes are involved

in this process, the voltage gated pentameric dihydropyridine receptor located in the TTS (encoded by the *CACNA1S* gene and accessory subunits encoded by *CACNA2D1*, *CACNG1*, *CACNB1*) and the homotetrameric ryanodine receptor of the SR (encoded by the *RYR1* gene). The voltage gated Ca^{2+} channel is activated by membrane depolarization and by this, activates the ryanodine receptor by direct protein/protein interaction which in turn releases Ca^{2+} into the cytosol [for review see 46].

Channel structure

The basic motif of the main cation channel subunit, the socalled á subunit, is a tetramic association of a series of 6 transmembrane α-helical segments, numbered S1-S6, connected by both intracellular and extracellular loops, the interlinkers (Figs. 1, 2). The α subunit contains the forming the ion-conducting pore and therefore determines the main characteristics of the cation channel complex conveying ion selectivity, voltage sensitivity, pharmacology and binding characteristics for endogenous and exogenous ligands. While for Ca^{2+} and Na^+ channels the α subunit consists of a momomer, K^+ channels form homo- or heteromultimers because each

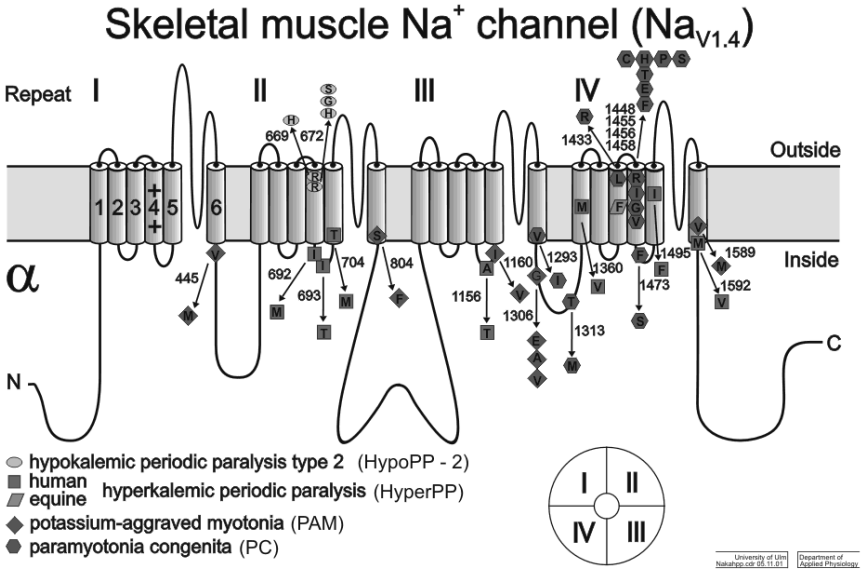

Fig. 1 Membrane topology model of the voltage-gated sodium channel of skeletal muscle. The a subunit functions as ion-conducting channel and consists of four highly homologous domains (repeats I–IV) containing six transmembrane segments each (S1–S6). The S6 transmembrane segments and the S5–S6 loops form the ion selective pore, and the S4 segments contain positively charged residues conferring voltage dependence to the protein. The repeats are connected by intracellular loops; one of them, the III–IV linker, contains the supposed inactivation particle of the channel. When inserted in the membrane, the four repeats of the protein fold to generate a central pore as schematically indicated on the right-hand bottom of the figure. The different symbols used for the known mutations leading to potassium-aggravated myotonia, paramyotonia congenita or two types of periodic paralysis are explained bottom left-hand . Conventional 1-letter abbreviations were used for replaced amino acids.

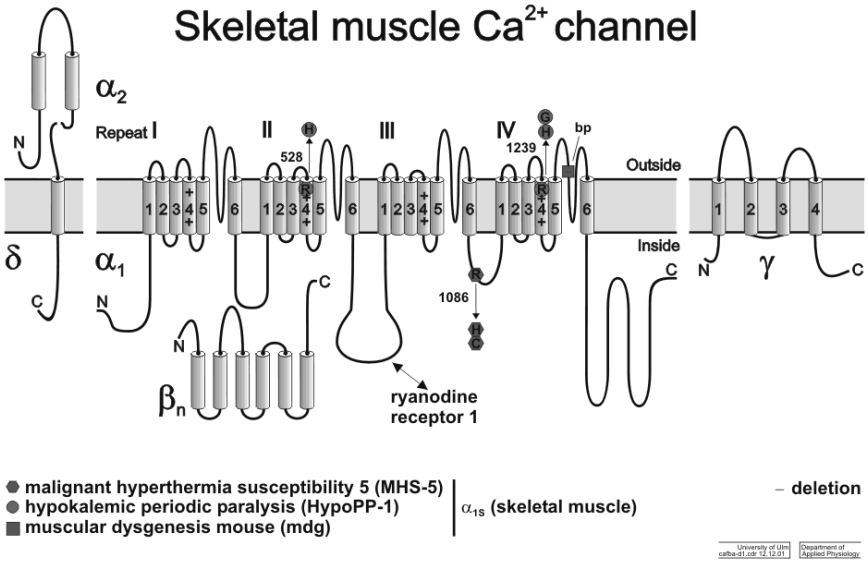

Fig. 2 Subunits of the voltage-gated calcium channel. The α1 subunit resembles α of the sodium channel however the function of the various parts, e. g. the III–IV linker, may not be the same. α2/δ, β1 to β4, and g are auxilliary subunits. Mutations in the α1S subunit shown here of the skeletal muscle L-type calcium channel (= dihydropyridine receptor, DHPR) have been described for man (HypoPP, MHS5) and mice (mdg). Conventional 1-letter abbreviations are used for the replaced amino acids. The symbols indicate the diseases as explained at the bottom of the left-hand side.

α subunit consists only of one domain with 6 transmembrane helices. Accessory subunits called beta, gamma, or delta do not share a common structure, some having one to several transmembrane segments and others being entirely intra- or extracellular. Functionally, they may influence channel expression, trafficking, and gating.

Voltage sensitive cation channels have at least one open state and at least two closed states, one from which the channel can directly be activated (the resting state) and one from which it cannot (the inactivated state). This implies that there are at least two gates regulating the opening of the pore, an activation and an inactivation gate, both of which are usually mediated by the α subunit (Fig. 3). Activation, inactivation and recovery from the inactivated state are voltage- and time-dependent processes.

The voltage sensitivity of cation channels is conveyed by the S4 segments which are thought to move outward upon depolarization and channel opening. During channel closing, not all voltage sensors move back at once generating a variety of closed states explaining the distribution of voltage sensor mutations to phenotypes in Na^+ channels. The ion conducting pore is thought to be lined by the S5-S6 interlinkers which contain the selectivity filter. While the localization of the activation gate may well be within the pore, the inactivation gate has been shown to be located in different regions in the Na^+ and K^+ channels.

Although recent X-ray data have elucidated the structure of the ClC chloride channel [16], not much about the structure/function relationship of Cl^- channels is known (Fig. 4). The homodimeric channel complex of skeletal muscle is encoded by *CLCN1* and conducts over the whole physiological voltage range.

Ryanodine receptors are among the largest known proteins consisting of homotetramers each over 5.000 amino acids long with a molecular mass of about 565 kDa. Morphological studies have revealed a quatrefoil structure with the hydrophobic parts of the four subunits forming a membrane spanning baseplate and the hydrophilic segments forming a cytoplasmic domain, the foot, which bridges the gap between T-tubular and SR membrane (Fig. 5).

Channelopathies

Clinically, skeletal muscle ion channelopathies appear as recurring episodes of muscle stiffness or weakness triggered by typical circumstances such as cold, exercise, oral K^+ load, or drugs. Muscle stiffness, termed myotonia, ameliorates by exercise and can be associated with transient weakness during quick movements lasting only for seconds. On the contrary, paradoxical myotonia or paramyotonia worsens with exercise and cold and is followed by long spells of limb weakness lasting from hours to days. According to the mode of transmission and K^+ sensitivity, four forms of myotonia and paramyotonia may be distinguished: dominant K^+-aggravated myotonia (PAM), dominant K^+-insensitive myotonia congenita, recessive generalised myotonia congenita, and paramyotonia congenita (PC). Myotonia is the clinical phenotype brought about by uncontrolled repetitive firing of action potentials leading to involuntary muscle contraction.

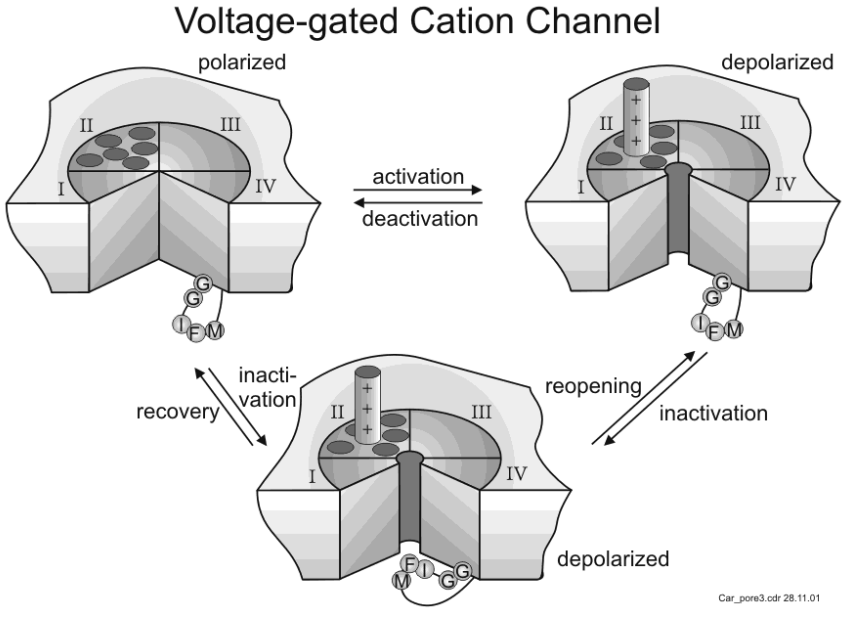

Fig. 3 Hinged-lid model of fast inactivation of sodium channels. Bird's eye view of the channel consisting of four similar repeats (I to IV). The channel is shown cut and spread open between repeats I and IV to allow a view of the intracellular loop between repeats III and IV. The loop acts as the inactivation gate whose hinge GG (a pair of glycines) allows it to swing between two positions, i. e. the open channel state and the inactivated closed state where the inactivation particle IFM (the amino acids isoleucine, phenylalanine and methionine) binds to its acceptor (the indicated amino acids are specific for the Na^+ channel).

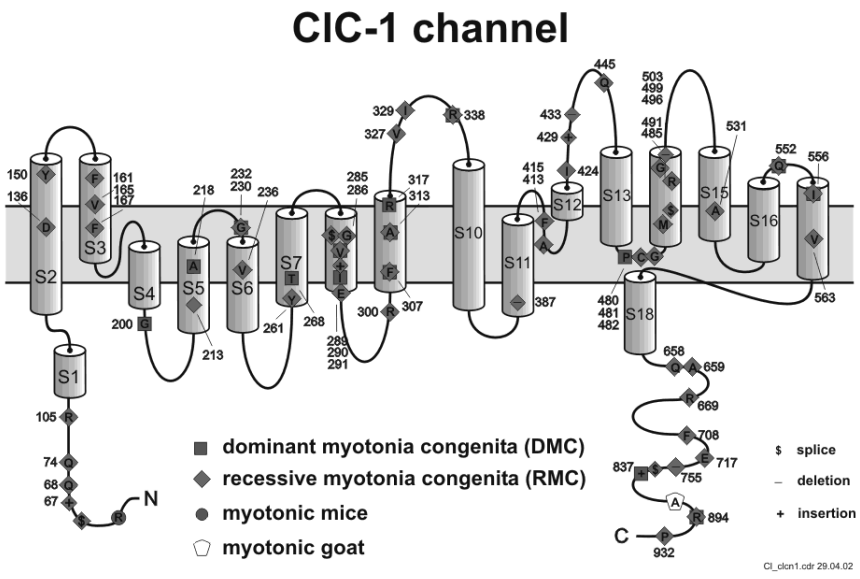

Fig. 4 Membrane topology model of the skeletal muscle chloride channel monomer, ClC-1, modified after [16]. The functional channel is a homodimer. The different symbols used for the known mutations leading to dominant Thomsen-type myotonia and recessive Becker-type myotonia are explained on the left-hand bottom. Conventional 1-letter abbreviations were used for replaced amino acids.

The contrary, lack of action potentials or inexcitability results in muscle weakness. Two dominant episodic types of weakness with or without myotonia are distinguished by the serum K^+ level during the attacks of tetraplegia: hyper- and hypokalemic periodic paralysis (HyperPP and HypoPP). Lastly, one dominant pharmacogenetic predisposition to react unfavorably upon administration of depolarizing muscle relaxants and volatile anesthetics during anesthesia, susceptibility to malignant hyperthermia, is also a voltage gated ion channelopathy. An acute, potentially lethal crisis is characterized by muscle hypermetabolism, rhabdomyolysis, body temperature elevation, muscle rigidity, and cardiac arrhythmia. MH is pathogenetically based on an uncontrollable intracellular Ca^{2+} release via the ryanodine receptor.

Myotonia and paramyotonia

Muscle stiffness, termed myotonia, ameliorates by exercise (warm-up phenomenon) and can be associated with transient weakness during quick movements lasting only for seconds. On the contrary, paradoxical myotonia or paramyotonia worsens with exercise and cold and is followed by long spells of limb weakness lasting from hours to days. Both are associated with muscle hypertrophy especially of the lower limbs. Clinically, they are distinguished according to the mode of transmission and K^+ sensitivity: dominant K^+-aggravated myotonia fluctuans [59, 60] and permanens [41], dominant K^+-insensitive myotonia congenita [71], recessive generalised myotonia [4], and paramyotonia congenita [17].

Molecular pathogenesis

Both myotonia and paramyotonia are brought about by uncontrolled repetitive firing of action potentials of the sarcolemma following an initial voluntary activation. This may be noted as a myotonic burst in the electromyogram. The involuntary electrical activity prevents the muscle from immediate relaxation after contraction which the patients experience as muscle stiffness. Basic pathology of the myotonic reaction in Thomsen and Becker myotonia is a reduced chloride conductance that fails to sufficiently buffer the after-depotential and triggers new premature action potentials [2, 44, 64]. In paramyotonia and potassium-aggravated myotonia, the increased sarcolemmal excitability is due to inactivation defects of the Na^+ channels that mediate the upstroke of the action potential [36, 37]. This results in channel re-openings and intracellular Na^+ accumulation which depolarises the muscle cells and thus elicits additional action potentials.

Chloride channel myotonias Thomsen and Becker

The Cl^- channel consists of a homodimer encoded by the *CLCN1* gene on chromosome 7q [34]. Both missense mutations (exchange of single amino acid residues) and nonsense mutations (alternative protein splicing or premature truncation) have been identified [21, 22, 26, 39]. While splicing mutations always lead to the recessive phenotype, various truncations and missense mutations are found in the Thomsen and Becker myotonia (Fig. 4). A few intermediate mutations are even able to generate both modes of transmission depending on supplemental genetic or environmental factors. Functionally, the

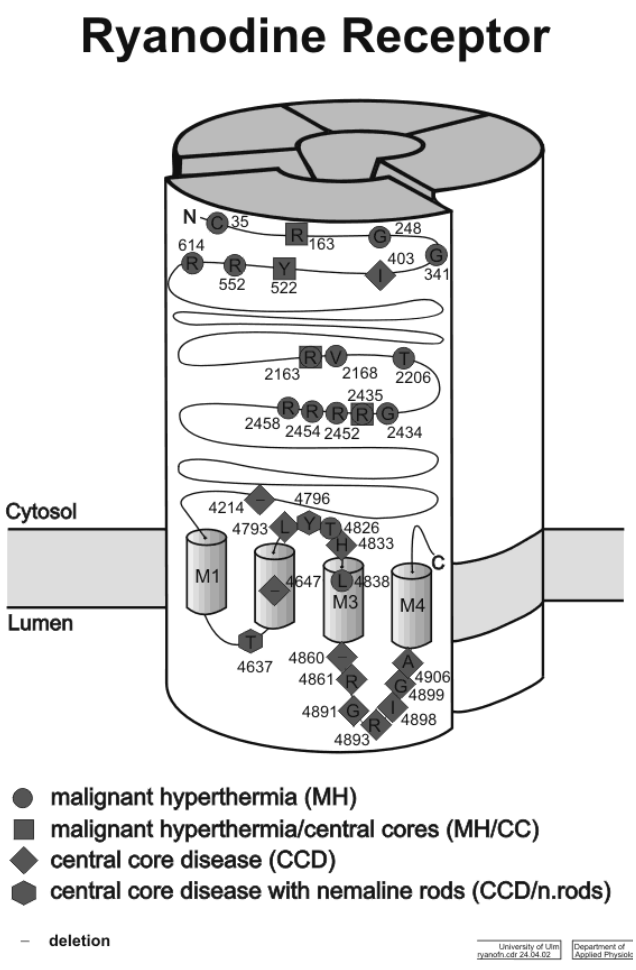

Fig. 5 Diagram of the homotetrameric ryanodine receptor, the calcium release channel situated in the membrane of the sarcoplasmic reticulum (SR). The cytosolic part of the protein complex, the so-called foot, bridges the gap between the transverse tubular system and the SR. Mutations have been described for the skeletal muscle ryanodine receptor (RyR1), which cause susceptibility to malignant hyperthermia (MHS) and central core disease (CCD). Conventional 1-letter abbreviations are used for the replaced amino acids.

dominant mutants exert a so-called dominant negative effect on the dimeric channel complex as shown by co-expression studies meaning that mutant/mutant *and* mutant/wildtype complexes are mal-functional. The most common feature of the Cl^- currents that result is a shift of the activation threshold towards more positive membrane potentials almost out of the physiological range [57, 76]. As a consequence of this, the Cl^- conductance is drastically reduced in the crucial vicinity of the resting membrane potential. This is not the case for the recessive mutants which do not functionally hinder the co-associated subunit, thus supplying the explanation why then two mutant alleles are required to reduce Cl^- conductance so much that myotonia develops, at least down to 30 % [52].

This knowledge has led to a double barrel model of the Cl^- channel with two independent ion conducting pores each with a fast opening mechanism of its own that is affected by the recessive mutations, but with a common slow additional gate structure shared with the co-associated subunit that is affected by the dominant mutations [66]. Intriguingly, this model has been confirmed by cryo-electron microscopy on two-dimensional protein crystals [48].

Sodium channel myotonia and paramyotonia

In K^+-aggravated myotonia and paramyotonia there is a gating defect of the Na^+ channels destabilizing the inactivated state, i. e. channel inactivation may be slowed or incomplete [12, 37, 41, 49, 77]. This results in an increased tendency of the muscle fibers to depolarise which generates action potentials and myotonia [37, 42]. It does not necessarily additionally affect channel activation because the pore-occluding gate structures decisive for activation and inactivation are located in different regions of the protein. Because the mutant channels exert an effect on cell excitability, the mutations produce a dominant change or gain-of-function.

One hot spot for the paramyotonia mutations is a special voltage-sensing transmembrane region [5, 42, 54] that couples channel inactivation to channel activation [12]; another hot spot is an intracellular protein loop containing the inactivation particle [47]. The K+-aggravated myotonia mutations are found in intracellular regions of the protein potentially interfering with the channel inactivation process (Fig. 1). Corresponding to the severity of the disruption of the inactivation gate structure on the protein level, there are three clinical severities to be distinguished [41, 49]: 1.) myotonia fluctuans where patients may not be aware of their disorder, 2.) myotonia responsive to acetazolamide [56] with a Thomsen-like clinical phenotype, and 3.) myotonia permanens with continuous electrical myotonia leading to a generalized muscle hypertrophy including face and neck muscles suggestive of facial dysmorphia. In all three types, body exertion or administration of depolarising agents may result in a severe or even life-threatening myotonic crisis [25, 41, 60, 74].

Therapy

Many myotonia patients can manage their disease without medication. Should treatment be necessary, myotonic stiffness responds well to drugs that reduce the increased excitability of the cell membrane by interfering with the Na^+ channels, i. e. local anaesthetics, antifibrillar and antiarrhythmic drugs, and related agents. These drugs suppress myotonic runs by decreasing the number of available Na^+ channels and have no known effect on Cl^- channels. Of the many drugs tested that can be administered orally, mexiletine is the drug of choice.

It also very effectively prevents weakness in paramyotonia congenita, probably by stabilizing the inactivated channel state.

Diagnosing strategy

Given a clinical diagnosis of myotonia by electromyographic examination, the first step is to exclude myotonic dystrophy. This can be performed by a genetic test from EDTA whole blood because the underlying mutation is known: an unphysiological expansion of a trinucleotide CTG repeat in the 3' untranslated region of the gene encoding a serine/threonine kinase on chromosome 19q. If exclusion is successful, usually there is no need for a muscle biopsy because 1.) the diagnosis can be less invasively confirmed by a genetic blood test, 2.) an effective therapy exists, 3.) the prognosis i. e. especially the development of permanent weakness cannot be influenced by therapy, and 4.) no specific changes are to be expected that influence therapy or prognosis.

Perspectives

From the pathogenetic viewpoint, several clinical phenomena are not yet fully understood indicating that there could be secondary alterations in muscle of myotonic patients functionally and subsequently morphologically: 1.) the warm-up phenomenon i. e. amelioration of the myotonia with exercise is not explainable by the Cl^- or Na^+ channel dysfunction [6], 2.) exactly which factors decide what mode of inheritance the four Cl^- channel mutations that can produce either the Thomsen or Becker phenotype will follow, 3.) what pathomechanism underlies the few recessive mutations that do not lead to Cl^- conductance reduction when functionally expressed, 4.) what generates the temperature dependence in paramyotonia congenita (but not in the allelic K^+-aggravated myotonia).

Dyskalemic periodic paralyses

Inexcitability due to lack of action potentials results in muscle weakness. Two dominant episodic types of weakness with or without myotonia are distinguished by the serum K^+ level during the attacks of tetraplegia: hyper- and hypokalemic periodic paralysis. In general, the hyperkalemic variant has an earlier onset and more frequent attacks, but these are much shorter and milder than in the hypokalemic form [20]. In contrast, the hypokalemic variant more frequently results in degenerative myopathy and permanent disabling weakness of the limbs and is never associated with myotonia like the hyperkalemic variant [7, 43]. Intake of K^+ and glucose have opposite effects in the two disorders: while K^+ triggers a hyperkalemic attack and glucose is a remedy, glucose provokes hypokalemic attacks which are ameliorated by K^+ intake.

Molecular pathogenesis

As above, the basis of the myotonia in the hyperkalemic variant is uncontrolled repetitive firing of action potentials and the underlying defect is a non-inactivating Na^+ inward current [36] through the tetrodotoxin-sensitive Na^+ channel encoded by SCN4A [18]. While Na^+ influx at slight depolarization itself generates action potentials and myotonia, stronger depolarizations lead to general inactivation of Na^+ channels both of mutant and the wildtype population (in a dominant disorder, both a mutant and a wildtype allele are present) and thus, weakness. The various mutations are situated at several disseminated intracellularly faced positions [53, 61, 75] potentially involved in generating parts of the inactivation apparatus or steric hindrance of its proper function (Fig. 1; for review see 40]. The mutations disturb channel inactivation and produce a persistent sodium current [10, 13, 14, 36, 38, 62]. Based on the same mechanism of pathogenesis and distribution of mutations, the reader may draw two conclusions, both of which are correct: 1.) there could be an overlapping of the phenotypes of hyperkalemic periodic paralysis with paramyotonia congenita and K^+-aggravated myotonia disorders, and 2.) more severe membrane depolarization found in periodic paralysis may result in more severe morphological findings.

In contrast to the gain of function changes associated with hyperkalemic periodic paralysis, hypo…-kalemic periodic paralysis is associated with a loss-of-function defect of three different ion channel types: Na^+, Ca^{2+}, and K^+ [1, 9, 19, 29, 32, 55, 69]. In the former two channels, the mutations are located solely in special transmembrane voltage-sensing segments (Figs. 1 and 2). In the latter, the sole reported mutation is situated in the accessory β subunit not containing the ion-conducting pore but influencing the gating properties thereof. Functionally, the inactivated state is stabilised in the Na^+ channel mutants [31, 35, 70], while the channel availability is reduced for the Ca^{2+} channel mutants [30, 51]. It is still a mystery however, how the loss-of-function mutations of these two cation channels can produce the long lasting depolarisation leading to the weakness [63, 65], but it does imply that a concomitant myotonia is not to be expected as is the case. In contrast, for the very rare K^+ channel variant, a reduced current density has been demonstrated that produces a slight membrane depolarization when heterologously expressed in a muscle cell line [1]. This would explain pathogenesis because the K^+ channel complex is thought to be essential for re-establishing and holding the highly negative resting potential of skeletal muscle fibres after the action potential.

Therapy

Local anesthetics and antiarrhythmic drugs of class I, such as mexiletine and lidocaine derivatives, are antimyotonic agents because they stabilise the inactivated state and lead to the phenomenon called use dependent block. Because the spontaneous attacks of weakness typical of hyperkalemic periodic paralysis are not influenced by mexiletine [58] (because no repetitive action potentials occur that can attenuated by a use dependent block), diuretics such as hydrochlorothiazide and acetazolamide can be administered. These drugs decrease frequency and severity of paralytic episodes by lowering serum K^+ and other so far unexplained favorable properties, e. g. influencing myoplasmic pH and plasmalemmal K^+ channels [73]. Therapeutically, long term low dose intake of acetazolamide is also recommended to avoid attacks of weakness in the hypokalemic variant. During acute hypokalemic paralysis phases though, oral K^+ administration has proved to relieve symptoms.

Perspectives

From the pathogenetic viewpoint, several clinical phenomena are not yet fully understood, indicating that there could be secondary alterations in muscle of periodic paralysis patients functionally and subsequently morphologically: 1.) why does one frequent hyperkalemic periodic paralysis mutation (T704M) cause severe myopathy with permanent weakness and the others do not, 2.) what is the pathophysiological mechanism linking a Ca^{2+} mutation to membrane depolarisation and paralysis when the channel does not contribute to the action potential, 3.) why does the hypokalemia cause depolarisation in patients with hypokalemic periodic paralysis when it hyperpolarises normal muscle, 4.) why does the loss-of-function Na^+ channel mutation produce episodic weakness instead of permanent weakness only.

Malignant hyperthermia and central core disease, two other calcium channel disorders

Malignant hyperthermia (MH)

MH susceptibility is an autosomal dominantly transmitted predisposition of clinically inconspicuous individuals to respond with uncontrollable skeletal muscle hypermetabolism upon exposure to volatile anesthetics or depolarizing muscle relaxants [15]. The triggering substances lead to an increase in the concentration of free myoplasmic calcium which is released from the sarcoplasmic reticulum calcium stores via the muscle ryanodine receptor channel [27]. During a MH reaction, a massive myoplasmic calcium release is induced, leading to muscle contracture especially of the masseter, generalized rigidity, and heat production. Hypermetabolism associated with the sarcoplasmic Ca^{2+} elevation upregulates glycogenolysis resulting in excess lactate production, metabolic acidosis, and hyperactivation of the oxidative cycle with increased ATP depletion, high oxygen consumption and carbon dioxide production with hypoxemia and hypercapnia. Tachycardia may be observed as an early sign. During the course of the crisis, rhabdomyolysis occurs with subsequent creatine kinase elevation, hyperkalemia potentially leading to ventricular fibrillation, and myoglobinuria with the possibility of renal failure. Hyperthermia may be a late sign in some cases. If an episode is survived, normalization of edematous muscle and creatine kinase levels occur within 10–15 days. For diagnosis of MH susceptibility, a functional test on skeletal muscle biopsy, the in vitro contracture test (IVCT), can be performed which reveals high concordance with the genetic phenotype [8].

Molecular pathogenesis

In the majority of families, linkage to the gene encoding the skeletal muscle ryanodine receptor, RyR1, a calcium channel is which under the control of the voltage-dependent dihydropyridine-sensitive L-type Ca^{2+} channel of skeletal muscle, can be found. To date, more than 20 disease-causing point mutations in RyR1 have been identified in man, most situated in the cytoplasmic part, the foot, of the protein (Fig. 5) [for review see 31]. The base of the homotetrameric protein, is located in the membrane of the sarcoplasmic reticulum, and forms the ion-conducting pore. Functionally, hypersensitivity of RyR1 to anesthetic triggering agents has been shown to be pathogenetically causative in functional tests of both muscle, isolated native proteins, and heterologously expressed full-length receptors [11]. Therapeutically, during an anesthetic crisis, dantrolene, an RyR1 inhibitor, is very effective, reducing the mortality rate from former 70 % to currently 10 %.

MH can be very highly heterogenous with 5 additional chromosomal loci mapped so far. However, only for one (MH susceptibility type 5) of these loci has a causative gene been identified, *CACNA1S*, so that this very rare type of MH is allelic to hypokalaemic periodic paralysis type 1 (HypoPP–1). In contrast to the voltage sensor mutations specific for HypoPP–1 (and HypoPP–2), the two mutations so far described for MH are situated in the myoplasmic loop connecting repeats III and IV the function of which is unknown (Fig. 2). The two mutations underline the functional link between RyR1 and the DHPR in excitation-contraction coupling [40, 50].

Central core disease (CCD)

CCD is a congenital myopathy often associated with skeletal anomalies [68]. Pathognomonic is the abundance of central cores along type 1 muscle fiber. CCD is often associated with MH susceptibility [67], and allelic to the RyR1 gene locus of MH [23, 33]. The myopathy is characterized by congenital muscle hypotonia (floppy infant syndrome), proximally pronounced weakness, delayed motor development, and slight CK elevation. In addition skeletal anomalies such as congenital hip displacement and scoliosis are frequent. Later in life, muscle strength usually improves except for rare cases showing progressive muscle weakness. It is one of the rare known myopathies for which strong physical exercise seems to be beneficial [24] although exercise-induced muscle cramps are often reported. Autosomal dominant inheritance is highly predominant and although several sporadic cases have been reported, a clear recessive trait has not been demonstrated yet. The clinical expression of the disease is highly variable. Not all mutation carriers in a family may develop this myopathy but instead may only have the MH trait [28].

Molecular pathogenesis

Except for one mutation, all are situated in the C-terminus of the RyR1 protein thought to form the channel pore region (Fig. 5). Expression of these mutations in non-muscle cells led to the finding of a leaky Ca^{2+} release channel compatible with the view of a myoplasmic Ca^{2+} overload responsible for the mitochondrial and cell damage [45, 72]. Recently a selective disruption of the orthograde excitation-contraction coupling process has been found in a skeletal muscle expression system suggesting a dominant negative effect of the CCD mutations on the voltage-controlled Ca^{2+} release [3]. This functional disruption may contribute to the muscle weakness and atrophy experienced by the patients.

Perspectives

From the pathogenetic viewpoint, the high intrafamilial variability of clinical expression and the association with skeletal anomalies are not yet fully understood. If a recessive form exists is still unclear. Thorough examination of family members including additional symptoms and signs as well as a thorough ultrastructure of muscle fibers including longitudinal sections may help to answer these questions. Of interest is also the question if clinical amelioration of weakness during life results from muscle regeneration or from compensation by unaffected muscles, and if the former holds true whether or not central cores, once developed can disappear in further course.

References

1. Abbott GW, Butler MH, Bendahhou S, Dalakas MC, Ptacek LJ, Goldstein SA (2001) MiRP2 forms potassium channels in skeletal muscle with Kv3.4 and Is associated with periodic paralysis. Cell 104: 217–231
2. Adrian RH, Bryant SH (1974) On the repetitive discharge in myotonic muscle fibres. J Physiol (London) 240: 505–515
3. Avila G, O'Brien JJ, Dirksen RT (2001) Excitation-contraction uncoupling by a human central core disease mutation in the ryanodine receptor. Proc Natl Acad Sci USA 98: 4215–4220
4. Becker PE (1977) Myotonia Congenita and Syndromes Associated with Myotonia. Thieme, Stuttgart
5. Bendahhou S, Cummins TR, Kwiecinski H, Waxman SG, Ptacek LJ (1999) Characterization of a new sodium channel mutation at arginine 1448 associated with moderate Paramyotonia congenita in humans. J Physiol (London) 518: 337–344
6. Birnberger KL, Klepzig M (1979) Influence of extracellular potassium and intracellular pH on myotonia. J Neurol 222: 23–35
7. Bradley WG, Taylor R, Rice DR (1990) Hausmanowa-Petruzewicz I, Adelman LS, Jenkison M, Jedrzejowska H, Drac H, Pendlebury WW. Progressive myopathy in hyperkalemic periodic paralysis. Arch Neurol 47: 1013–1017
8. Brandt A, Schleithoff L, Jurkat-Rott K, Klingler W, Baur C, Lehmann-Horn F (1999) Screening of the ryanodine receptor gene in 105 malignant hyperthermia families: novel mutations and concordance with the in-vitro contracture test. Hum Mol Gen 8: 2055–2062
9. Bulman DE, Scoggan KA, Van Oene MD, Nicolle MW, Hahn AF, Tollar LL, Ebers GC (1999) A novel sodium channel mutation in a family with hypokalemic periodic paralysis. Neurology 53: 1932–1936
10. Cannon SC, Strittmatter SM (1993) Functional expression of sodium channel mutations identified in families with periodic paralysis. Neuron 10: 317–326
11. Censier K, Urwyler A, Zorzato F, Treves S (1998) Intracellular calcium homeostasis in human primary muscle cells from malignant hyperthermia-susceptible and normal individuals. Effect of overexpression of recombinant wild-type and Arg163Cys mutated ryanodine receptors. J Clin Invest 101: 1233–1242
12. Chahine M, George AL Jr, Zhou M, Ji S, Sun W, Barchi RL, Horn R (1994) Sodium channel mutations in paramyotonia congenita uncouple inactivation from activation. Neuron 12: 281–294
13. Cummins TR, Sigworth FJ (1996) Impaired slow inactivation of mutant sodium channels. Biophys J 71: 227–236
14. Cummins TR, Zhou J, Sigworth FJ, Ukomadu C, Stephan M, Ptacek LJ, Agnew WS (1993) Functional consequences of a Na+ channel mutation causing hyperkalemic periodic paralysis. Neuron 10: 667–678
15. Denborough MA, Lovell RRH (1960) Anesthetic deaths in a family. Lancet ii: 45

16. Dutzler R, Campbell EB, Cadene M, Chait BT, MacKinnon R (2002) X-ray structure of a ClC chloride channel at 3.0 A reveals the molecular basis of anion selectivity. Nature 415: 287–294
17. Eulenburg A (1886) Über eine familiäre durch 6 Generationen verfolgbare Form kongenitaler Paramyotonie. Neurol Zentralbl 5: 265–272
18. Fontaine B, Khurana TS, Hoffman EP, Bruns GA, Haines JL, Trofatter JA, Hanson MP, Rich J, McFarlane H, Yasek DM, Romano D, Gusella JF, Brown RH Jr (1990) Hyperkalemic periodic paralysis and the adult muscle sodium channel a-subunit gene. Science 250: 1000–1002
19. Fontaine B, Vale Santos JM, Jurkat-Rott K, Reboul J, Plassart E, Rime CS, Elbaz A, Heine R, Guimaraes J, Weissenbach J, Baumann N, Fardeau M, Lehmann-Horn F (1994) Mapping of the hypokalaemic periodic paralysis (HypoPP) locus to chromosome 1q31–32 in three European families. Nature Genet 6: 267–272
20. Gamstorp I (1956) Adynamia episodica hereditaria. Acta Paediat Scand 45 (suppl 108): 1–126
21. George AL Jr, Crackover MA, Abdalla JA, Hudson JA, Ebers GC (1993) Molecular basis of Thomsen's disease (autosomal dominant myotonia congenita). Nature Genet 3: 305–310
22. George AL Jr, Sloan-Brown K, Fenichel GM, Mitchell GA, Spiegel R, Pascuzzi RM (1994) Nonsense and missense mutations of the muscle chloride channel gene in patients with myotonia congenita. Hum Mol Genet 3: 2071–2072
23. Haan EA, Freemantle CJ, McCure JA, Friend KL, Mulley JC (1990) Assignment of the gene for central core disease to chromosome 19. Hum Genet 86: 187–190
24. Hagberg JM, Carroll JE, Brooke MH (1980) Endurance exercise training in a patient with central core disease. Neurology 30: 1242–1244
25. Heine R, Pika U, Lehmann-Horn F (1993) A novel SCN4A mutation causing myotonia aggravated by cold and potassium. Hum Mol Genet 2: 1349–1353
26. Heine R, George AL, Pika U, Deymeer F, Rüdel R, Lehmann-Horn F (1994) Proof of a non-functional muscle chloride channel in recessive myotonia congenita (Becker) by detection of a 4 base pair deletion. Hum Mol Genet 3: 1123–1128
27. Iaizzo PA, Klein W, Lehmann-Horn F (1988) Fura-2 detected myoplasmic calcium and its correlation with contracture force in skeletal muscle from normal and malignant hyperthermia susceptible pigs. Pflügers Archiv – Eur J Physiol 411: 648–653
28. Islander G, Henriksson KG, Ranklev-Twetman E (1995) Malignant hyperthermia susceptibility without central core disease (CCD) in a family where CCD is diagnosed. Neuromusc Disord 5: 125–127
29. Jurkat-Rott K, Lehmann-Horn F, Elbaz A, Heine R, Gregg RG, Hogan K, Powers P, Lapie P, Vale-Santos JE, Weissenbach J, Fontaine B (1994) A calcium channel mutation causing hypokalemic periodic paralysis. Hum Mol Gen 3: 1415–1419
30. Jurkat-Rott K, Uetz U, Pika-Hartlaub U, Powell J, Fontaine B, Melzer W, Lehmann-Horn F (1998) Calcium currents and transients of native and heterologously expressed mutant skeletal muscle DHP receptor α1 subunits (R528H). FEBS Letters 423: 198–204
31. Jurkat-Rott K, McCarthy T, Lehmann-Horn F (2000) Genetics and pathogenesis of malignant hyperthermia. Muscle Nerve 23: 4–17
32. Jurkat-Rott K, Mitrovic N, Hang C, Kouzmenkin A, Iaizzo P, Herzog J, Lerche H, Nicole N, Vale-Santos J, Chauveau D, Fontaine B, Lehmann-Horn F (2000) Voltage sensor sodium channel mutations cause hypokalemic periodic paralysis type 2 by enhanced inactivation and reduced current. Proc Natl Acad Sci USA 97: 9549–9554
33. Kausch K, Lehmann-Horn F, Hartung EJ, Janka M, Wieringa B, Grimm T, Müller CR (1991) Evidence for linkage of the central core disease locus to the proximal long arm of human chromosome 19. Genomics 10: 765–769
34. Koch MC, Steinmeyer K, Lorenz C, Ricker K, Wolf F, Otto M, Zoll B, Lehmann-Horn F, Grzeschik KH, Jentsch TJ (1992) The skeletal muscle chloride channel in dominant and recessive human myotonia. Science 257: 797–800
35. Kuzmenkin A, Muncan V, Jurkat-Rott K, Hang C, Lerche H, Lehmann-Horn F, Mitrovic N (2002) Enhanced inactivation and pH sensitivity of Na^+ channel mutations causing hypokalemic periodic paralysis type II. Brain 125: 835–843
36. Lehmann-Horn F, Küther G, Ricker K, Grafe P, Ballanyi K, Rüdel R (1987a) Adynamia episodica hereditaria with myotonia: a non-inactivating sodium current and the effect of extracellular pH. Muscle Nerve 10: 363–374
37. Lehmann-Horn F, Rüdel R, Ricker K (1987b) Membrane defects in paramyotonia congenita (Eulenburg). Muscle Nerve 10: 633–641
38. Lehmann-Horn F, Iaizzo PA, Hatt H, Franke C (1991) Altered gating and conductance of Na^+ channels in hyperkalemic periodic paralysis. Pflügers Arch 418: 297–299
39. Lehmann-Horn F, Mailänder V, Heine R, George AL (1995) Myotonia levior is a chloride channel disorder. Hum Mol Gen 4: 1397–1402
40. Lehmann-Horn F, Jurkat-Rott K (1999)Voltage-gated ion channels and hereditary disease. Physiol Rev 79: 1317–1371
41. Lerche H, Heine R, Pika U, George AL, Mitrovic N, Browatzki M, Weiss T, Bastide-Rivet M, Franke C, LoMonaco M, Ricker K, Lehmann-Horn F (1993) Human sodium channel myotonia: Slowed channel inactivation due to substitutions for a glycine within the III/IV linker. J Physiol (London) 470: 13–22
42. Lerche H, Mitrovic N, Dubowitz V, Lehmann-Horn F (1996) Pathophysiology of paramyotonia congenita: The R1448P sodium channel mutation in adult human skeletal muscle. Ann Neurol 39: 599–608
43. Links TP, Zwarts MJ, Wilmink JT, Molenaar WM, Oosterhuis HJGH (1990) Permanent muscle weakness in familial hypokalaemic periodic paralysis. Brain 113: 1873–1889
44. Lipicky RJ(1979) Myotonic syndromes other than myotonic dystrophy. In: Handbook of Clinical Neurology vol. 40. Vinken, PJ & Bruyn GW, Editors. Elsevier, Amsterdam, pp 533–571
45. Lynch PJ, Tong J, Lehane M, Mallet A, Giblin L, Heffron JJ, Vaughan P, Zafra G, MacLennan DH, McCarthy TV (1999) A mutation in the transmembrane/luminal domain of the ryanodine receptor is associated with abnormal Ca^{2+}-release channel function and severe central core disease. Proc Natl Acad Sci USA 96: 4164–4169
46. MacKrill JJ (1999)Protein-protein interactions in intracellular Ca^{2+}-release channel function. Biochem J 337: 345–361
47. McClatchey AI, van den Bergh P, Pericak-Vance MA, Raskind W, Verellen C, McKenna-Yasek D, Rao K, Haines JL, Bird T, Brown RH Jr, Gusella JF (1992) Temperature-sensitive mutations in the III-IV cytoplasmic loop region of the skeletal muscle sodium channel gene in paramyotonia congenita. Cell 68: 769–774
48. Mindell JA, Maduke M, Miller C, Grigorieff N (2001) Projection structure of a ClC-type chloride channel at 6.5 A resolution. Nature 409: 219–223
49. Mitrovic N, George AL Jr, Lerche H, Wagner S, Fahlke Ch, Lehmann-Horn F (1995) Different effects on gating of three myotonia-causing mutations in the inactivation gate of the human muscle sodium channel. J Physiol (London) 487: 107–114

50. Monnier N, Procaccio V, Stieglitz P, Lunardi J (1997) Malignant-hyperthermia susceptibility is associated with a mutation of the a1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle. Am J Hum Genet 60: 1316–1325
51. Morrill JA, Cannon SC (1999) Effects of mutations causing hypokalaemic periodic paralysis on the skeletal muscle L-Type Ca^{2+} channel expressed in Xenopus laevis oocytes. J Physiol (London) 520: 321–336
52. Palade PT, Barchi RL (1977) On the inhibition of muscle membrane chloride conductance by aromatic carboxylic acids. J Gen Physiol 69: 879–896
53. Ptacek LJ, George AL Jr, Griggs RC, Tawil R, Kallen RG, Barchi RL, Robertson M, Leppert MF (1991) Identification of a mutation in the gene causing hyperkalemic periodic paralysis. Cell 67: 1021–1027
54. Ptacek LJ, George AL Jr, Barchi RL, Griggs RC, Riggs JE, Robertson M, Leppert MF (1992) Mutations in an S4 segment of the adult skeletal muscle sodium channel cause paramyotonia congenita. Neuron 8: 891–897
55. Ptacek LJ, Tawil R, Griggs RC, Engel A, Layzer RB, Kwiecinsky H, McManis PG, Santiago L, Moore M, Fouad G, Bradley P, Leppert MF (1994a) Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. Cell 77: 863–868
56. Ptacek LJ, Tawil R, Griggs RC, Meola G, McManis P, Barohn RJ, Mendell JR, Harris C, Spitzer R, Santiago F, Leppert MF (1994b) Sodium channel mutations in acetazolamide-responsive myotonia congenita, paramyotonia congenita and hyperkalemic periodic paralysis. Neurology 44: 1500–1503
57. Pusch M, Steinmeyer K, Koch MC, Jentsch TJ (1995) Mutations in dominant human myotonia congenita drastically alter the voltage dependence of the CIC–1 chloride channel. Neuron 15: 1455–1463
58. Ricker K, Böhlen R, Rohkamm R (1983) Different effectiveness of tocainide and hydrochlorothiazide in paramyotonia congenita with hyperkalemic episodic paralysis. Neurology 33: 1615–1618
59. Ricker K, Lehmann-Horn F, Moxley RT III (1990) Myotonia fluctuans. Arch Neurol 47: 268–272
60. Ricker R, Moxley RT, Heine R, Lehmann-Horn F (1994) Myotonia fluctuans, a third type of muscle sodium channel disease. Arch Neurol 51: 1095–1102
61. Rojas CV, Wang J, Schwartz L, Hoffman EP, Powell BR, Brown RH Jr (1991) A Met-to-Val mutation in the skeletal muscle sodium channel a-subunit in hyperkalemic periodic paralysis. Nature 354: 387–389
62. Rojas CV, Neely A, Velasco-Loyden G, Palma V, Kukuljan M (1999) Hyperkalemic periodic paralysis M1592V mutation modifies activation in human skeletal muscle Na + channel. Am J Physiol 276: C259–266
63. Rüdel R, Lehmann-Horn F, Ricker K, Küther G (1984) Hypokalemic periodic paralysis: in vitro investigation of muscle fiber membrane parameters. Muscle Nerve 7: 110–120
64. Rüdel R, Ricker K, Lehmann-Horn F (1988) Transient weakness and altered membrane characteristic in recessive generalized myotonia (Becker). Muscle Nerve 11: 202–211
65. Ruff RL (1999) Insulin acts in hypokalemic periodic paralysis by reducing inward rectifier K^+ current. Neurology 53: 1556–1563
66. Saviane C, Conti F, Pusch M (1999) The muscle chloride channel ClC–1 has a double-barreled appearance that is differentially affected in dominant and recessive myotonia. J Gen Physiol 113: 457–468
67. Shuaib A, Paasuke RT, Brownell KW (1987) Central core disease. Clinical features in 13 patients. Medicine 66: 389–396
68. Shy GM, Magee KR (1956) A new congenital non-progressive myopathy. Brain 79: 610–621
69. Sternberg D, Maisonobe T, Jurkat-Rott K, Nicole S, Launay E, Chauveau D, Tabti N, Lehmann-Horn F, Hainque B, Fontaine B (2001) Hypokalemic periodic paralysis type 2 caused by mutations at codon 672 in the muscle sodium channel gene SCN4A. Brain 124: 1091–1099
70. Struyk AF, Scoggan KA, Bulman DE, Cannon SC (2000) The human skeletal muscle Na channel mutation R669H associated with hypokalemic periodic paralysis enhances slow inactivation. J Neurosci 20: 8610–8617
71. Thomsen J (1876) Tonische Krämpfe in willkürlich beweglichen Muskeln in Folge von ererbter psychischer Disposition. Arch Psychiatr Nervenkrankh 6: 702–718
72. Tilgen N, Zorzato F, Halliger-Keller B, Muntoni F, Sewry C, Palmucci LM, Schneider C, Hauser E, Lehmann-Horn F, Muller CR, Treves S (2001) Identification of four novel mutations in the C-terminal membrane spanning domain of the ryanodine receptor 1: association with central core disease and alteration of calcium homeostasis. Hum Mol Genet 10: 2879–2887
73. Tricarico D, Barbieri M, Camerino DC (2000) Acetazolamide opens the muscular KCa^{2+} channel: a novel mechanism of action that may explain the therapeutic effect of the drug in hypokalemic periodic paralysis. Ann Neurol 48: 304–312
74. Vita GM, Olckers A, Jedlicka AE, George AL, Heiman-Patterson T, Rosenberg H, Fletcher JE, Levitt RC (1995) Masseter muscle rigidity associated with glycine1306-to-alanine mutation in adult muscle sodium channel a-subunit gene. Anesthesioly 82: 1097–1103
75. Wagner S, Lerche H, Mitrovic N, Heine R, George AL, Lehmann-Horn F (1997) A novel sodium channel mutation causing a hyperkalemic paralytic and paramyotonic syndrome with variable clinical expressivity. Neurology 49: 1018–1025
76. Wagner S, Deymeer F, Kürz LL, Benz S, Schleithoff L, Lehmann-Horn F, Serdaroglu P, Özdemir C, Rüdel R (1998) The dominant chloride channel mutant G200R causing fluctuating myotonia: clinical findings, electrophysiology, and channel pathology. Muscle Nerve 21: 1122–1128
77. Yang N, Ji S, Zhou M, Ptacek LJ, Barchi RL, Horn R, George AL Jr (1994) Sodium channel mutations in paramyotonia congenita exhibit similar biophysical phenotypes in vitro. Proc Natl Acad Sci USA 91: 12785–12789