Electrophysiology and molecular pharmacology of muscle channelopathies

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SUMMARY

As voltage-gated ion channels are essential for membrane excitation, it is not surprising that mutations in the respective channel genes cause diseases characterised by altered cell excitability. Skeletal muscle was the first tissue in which such diseases, namely the myotonias and periodic paralyses, were recognised as ion channelopathies. The detection of the functional defect that is brought about by the disease-causing mutation is essential for the understanding of the pathology. Much progress on the road to this aim was achieved by the combination of molecular biology and electrophysiological patch clamp techniques. The functional expression of the mutations in expression systems allows to study the functional alterations of mutant channels and to develop new strategies for the therapy of ion channelopathies, e.g. by designing drugs that specifically suppress the effects of malfunctioning channels.

Keywords: *Periodic paralysis • Myotonia • Electromyography • Andersen syndrome • Genetics • KCNE3*

RÉSUMÉ

Aspects électrophysiologiques et pharmacologie moléculaire des canalopathies musculaires.

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Les canaux ioniques voltage-dépendant étant essentiels à l'excitation membranaire, il n'est pas surprenant que les mutations de leurs gènes respectifs se caractérisent par une altération de l'excitabilité cellulaire. Le muscle squelettique est le premier tissu où des canalopathies ont été individualisées : myotonies, paralysies périodiques grâce à la biologie moléculaire et aux études électrophysiologiques de patch clamp. De nombreux progrès ont été réalisés dans la compréhension de la physiopathologie des affections. L'expression fonctionnelle des mutations dans certains systèmes permet l'étude des altérations fonctionnelles des canaux ioniques et le développement de nouvelles stratégies thérapeutiques.

Mots-clés : Paralysie périodique • Myotonie • Pharmacologie • Electromyographie • Syndrome d'Andersen • Génétique • KCNE3

INTRODUCTION

Skeletal muscle ion channel defects generally lead to abnormal muscle fibre excitation. Therefore, the ability to generate action potentials is either enhanced or decreased in the muscle ion channelopathies. Clinically, this results in phenotypes caused by muscle fibre membrane hyperexcitability leading to (myotonic) stiffness and/or in phenotypes associated with sarcolemmal inexcitability leading to (dyskalemic) weakness. These disorders belong to the so-called non-dystrophic myotonias and periodic paralyses. Symptoms occur only episodically with varying intervals of normal muscle function and excitation in between. Apparently, the ion channel defects are usually well-compensated and an additional, special endogenous or exogenous trigger is required for malfunction to become apparent.

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MYOTONIA

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 also called paramyotonia worsens with exercise and cold. Clinically, they are distinguished according to the sensitivity to potassium, exercise and cold environment. Myotonia congenita shows the warm-up phenomenon, is K^+-insensitive and separated according to its mode of transmission into the dominant form (Thomsen, 1876) and the recessive generalized myotonia (Becker, 1977). Myotonia fluctuans (Ricker *et al*., 1990; 1994), acetazolamide-responsive myotonia (Trudell *et al*., 1987; Ptacek *et al*., 1994b) and myotonia permanens (Lerche *et al*., 1993) - all dominantly inherited - are aggravated by potassium. Hyperkalemic periodic paralysis (Gamstorp, 1956) and paramyotonia congenita (Eulenburg, 1886) are associated with myotonia and also sensitive to potassium but is usually followed by long spells of flaccid weakness and will be therefore separately discussed.

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 electromyogramme. 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-potential and triggers new pre-mature action potentials (Adrian and Bryant, 1974; Lipicky, 1979; Rüdel *et al*., 1988). 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 (Lehmann-Horn *et al*., 1987a; 1987b). 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 (Koch *et al.*, 1992). Both missense mutations (exchange of single amino acid residues) alternative protein splicing and nonsense mutations (pre-mature truncation) have been identified (George *et al*., 1993; Heine *et al*., 1994; George *et al.*, 1994; Lehmann-Horn *et al*., 1995). While splicing mutations usually lead to the recessive phenotype, various truncations and missense mutations are found in the Thomsen and Becker myotonia. Functionally, the 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 malfunctional. The most common feature of the thereby resulting Cl^- currents is a shift of the activation threshold towards more positive membrane potentials almost out of the physiological range (Pusch *et al*., 1995; Wagner *et al*., 1998). 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 supplying the explanation why then two mutant alleles are required to reduce Cl^- conductance so much that myotonia develops (at least down to 30 %; Palade & Barchi, 1977).

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 (Saviane *et al*., 1999). Intriguingly, this model has been confirmed by cryo-electron microscopy on two-dimensional protein crystals (Mindell *et al*., 2001).

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 (Lehmann-Horn *et al*., 1987b; Lerche *et al*., 1993; Chahine *et al*., 1994; Yang *et al*., 1994; Mitrovic *et al*., 1995). This results in an increased tendency of the muscle fibres to depolarise which generates action potentials and myotonia (Lehmann-Horn *et al*., 1987b, Lerche *et al*., 1996). 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 (Ptacek *et al*., 1992; Lerche *et a*l., 1996; Bendahhou *et al*., 1999) that couples channel inactivation to channel activation (Chahine *et al*., 1994); another hot spot is an intracellular protein loop containing the inactivation particle (McClatchey *et al*., 1992). The K^+-aggravated myotonia mutations are found in intracellular regions of the protein potentially interfering with the channel inactivation process. Corresponding to the severity of the disruption of the inactivation gate structure on the protein level, there are three clinical severities to be distinguished (Lerche *et al*., 1993; Mitrovic *et al*., 1995): 1.) myotonia fluctuans where patients may not be aware of their disorder, 2.) myotonia responsive to acetazolamide (Ptacek *et al*., 1994b) 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 (Lerche *et al*., 1993; Heine *et al*., 1993; Ricker *et al*., 1994; Vita *et al*., 1995).

DYSKALEMIC EPISODIC WEAKNESS

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 (Gamstorp, 1956). 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 (Bradley *et al*., 1990; Links *et al*., 1990). 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.

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 (Lehmann-Horn *et al*., 1987a) through the tetrodotoxin-sensitive Na^+ channel encoded by SCN4A (*Table I*; Fontaine *et al*., 1990). 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 wild-type 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 (Rojas *et al*., 1991; Ptacek *et al*., 1991; Wagner *et al*., 1997) potentially involved in generating parts of the inactivation apparatus or steric hinderence of its proper function (for review see Lehmann-Horn and Jurkat-Rott, 1999). The mutations disturb channel inactivation and produce a persistent sodium current (Lehmann-Horn *et al*., 1987a; 1991; Cannon and Strittmatter, 1993; Cummins *et al*., 1993; Cummins and Sigworth, 1996; Rojas *et al*., 1999). 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 hyperkamelic 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 to hyperkalemic periodic paralysis, hypokalemic periodic paralysis is associated with a loss-of-function defect of two different ion channel types: Na^+ and Ca^{2+} (Bulman *et al*., 1999; Jurkat-Rott *et al*., 2000; Fontaine *et a*l., 1994; Jurkat-Rott *et al*., 1994). The mutations are located solely in special transmembrane voltage-sensing segments. Functionally, the inactivated state is stabilised in the Na^+ channel mutants (Jurkat-Rott *et al*., 2000; Struyk *et al*., 2000), while the channel availability is reduced for the Ca^{2+} channel mutants (Jurkat-Rott *et al*., 1998; Morrill and Cannon, 1999). 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 (Rüdel et al., 1984; Ruff, 1999), but it does imply that a concomitant myotonia is not to be expected as is the case.

An R83H point mutation in KCNE3-encoded MiRP2 protein, a potassium channel α subunit encoded by KCNE3, has been reported to cause 2% of familial periodic paralyses (Abbott *et al.,* 2001*).* Other studies indentified the mutation in the same percentage of healthy controls and provocation of R83H carriers with glucose or KC1 did not provoke weakness (Sternberg *et al*., 2003; Jurkat-Rott and Lehmann-Horn, 2004). Apparently KCNE3 is not a gene related to periodic paralysis. The Kir2.1 potassium channel responsible for the Andersen syndrome (clinical trias periodic paralysis, arrhythmia and dysmorphic features) functions as inward going rectifiers, i.e., it is essential for establishing the high negative resting membrane potential of muscle fibers and the repolarization phase of the cardiac action potential. The mutations causing Andersen's syndrome reduce this potassium current. A mutant monomer can exert a dominant negative effect on the entire multimeric complex which explains the dominant inheritance of the disease (Plaster *et al.*, 2001). The function of the muscle fibers may be normal at normokalemia because the membrane polarization is just negative enough that action potentials can be generated. During hypokalemia, however, the potassium level in the T tubules may decrease to values at which the sodium-potassium pump will be blocked and the T tubular membrane then further depolarizes and becomes inexcitable (Lehmann-Horn and Jurkat-Rott, unpublished data).

Pharmacology

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 stabilize the inactivated sodium channel state by shifting the steady-state inactivation curve to more negative potentials and slow recovery from inactivation (Fan *et al*., 1996; Fleischhauer *et al*., 1998; Desaphy *et al*., 2001). The shift of the voltage dependency decreases the number of sodium channels available for action potential generation, and the slowed recovery from inactivation prolongs the channel refractory period and accounts for the use-dependent block. They have no known effect on Cl^- channels. Of the many drugs tested that can be administered orally, mexiletine is the drug of choice. It is more beneficial in sodium channel than in chloride channel myotonia since it preferentially blocks the non-inactivating mutant sodium channels that reopen abnormally frequently. Mexiletine

also very effectively prevents weakness in paramyotonia congenita, probably by stabilizing the inactivated channel state. Unfortunately it cannot prevent weakness in hyperkalemic periodic paralysis.

As muscle weakness is caused by sarcolemmal depolarization and repolarizing the membrane to a normal resting potentials should recover muscle strength. *In vitro* experiments support this notion: exposure of a paralyzed muscle bundle of a HypoPP patient to cromakalim, a K_{ATP} potassium channel opener, restored muscle force of the fibers via a shift of the membrane potential to about -90 mV (Grafe *et al*., 1990). Other KATP potassium channel openers, such as diazoxide and pinacidil, were also effective *in vivo* and *in vitro* in preventing and relieving attacks of weakness (Johnsen, 1977; Ligtenberg *et al*., 1996). These drugs also inhibit insulin secretion, and have a higher specificity for smooth than skeletal muscle with marked effects on blood pressure; therefore their long term administration is best avoided. The development of potassium channel openers that act more specifically on skeletal muscle cannot be expected as the periodic paralyses are orphan diseases.

Acetazolamide is an alternative treatment of patients with sodium channel myotonias. The benefit of this drug can be judged from the fact that one of the sodium channel myotonias, was dubbed *acetazolamide-responsive myotonia* (Trudell *et al.*, 1987). Acetazolamide can improve paramyotonic stiffness (Benstead *et al.*, 1987) but may induce weakness in PC patients susceptible to cold-induced weakness (Griggs *et al*., 1978).

It is often advisable to prevent hyperkalemic attacks of weakness by the continuous use of a thiazide diuretic (Gamstorp, 1956) or the carbonic anhydrase inhibitors acetazolamide and dichlorophenamide (McArdle, 1962; Riggs *et al.*, 1981; Tawil *et al*., 2000). The beneficial effect of these diuretics is probably due to their capacity to lower the serum potassium level. Acetazolamide and hydrochlorothiazide (HTC) to a lesser extent can also exert a beneficial effect by inhibiting membrane-bound carbonic anhydrase IV; this lowers serum and myoplasmic pH and slows recovery from exercise-induced myoplasmic acidification (Lehmann-Horn *et al*., 1987a; Kowalchuk *et al.*, 2000; Wetzel *et al*., 2001). Other carbonic anhydrase IV inhibitors, like dichlorophenamide and those used as anti-epileptic drugs (sulthiame, topiramate), may be effective as well. As acetazolamide and HTC are activators of KATP and KCa^{2+} potassium channels (Tricarico *et al*., 2000) they may also exert a beneficial effects by stabilizing the resting membrane potential. Interestingly this action is similar to that of cromakalim (Grafe *et al*., 1990) and opposite of the effect of mexiletine which is not only a sodium channel blocker but also inhibits K_{ATP} channels of skeletal muscle. K_{ATP} channels are only open in the absence of (regional) ATP and are widely known to be inhibited by glibenclamide and other antidiabetic drugs.

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