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State of the art in hereditary muscle channelopathies

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A combination of electrophysiological and genetic studies has resulted in the identification of several skeletal muscle disorders to be caused by pathologically functioning ion channels and has led to the term channelopathies. Typical hereditary muscle channelopa thies are congenital myasthenic syndromes, non-dystrophic myotonias, periodic paralyses, malignant hyperthermia, and central core disease. Most muscle channelopathies are commonly considered to be benign diseases. However, life-threatening weakness episodes or progressive permanent weakness may make these diseases severe, particularly the periodic paralyses (PP). Even in the typical PP forms characterized by episodic occurrence of weakness, up to 60% of the patients suffer from permanent weakness and myopathy with age. In addition, some PP patients present with a predominant progressive muscle weakness phenotype. The weakness can be explained by strongly depolarized fibers that take up sodium and water and that are electrically inexcitable. Drugs that repolarize the fiber membrane can restore muscle strength and may prevent progression.

Key words: Congenital myasthenic syndromes, non-dystrophic myotonias, periodic paralyses, susceptibility to malignant hyperthermia, central core disease

Introduction

Most muscle channelopathies have similar clinical features: typically the symptoms occur as episodes which last from minutes to days and show spontaneous and complete remission and onset in the first or second decade of life. Frequently the symptoms can be aggravated by exercise, rest following physical activity, hormones, mental stress, or certain types of food and drugs. Some patients show amelioration at the age of 40 or 50 (1). Therefore muscle channelopathies are commonly considered to be benign diseases. However, severe muscle stiffness and transient weakness in some forms of myotonia, and spontaneous attacks of paralysis in PP drastically reduce the patient's ability to perform activities of daily living. The inherent danger of cardiac arrhythmia due to excessive hypo- or hyperkalemia aggravates the situation in these patients. Since patients with muscle channelopathies may not have any interictal features or the weakness may be misinterpreted, they are often thought to have had a conversion reaction, and this may cause them to suffer needlessly. Up to 60% of the periodic paralysis patients develop a progressive myopathy with age resembling limb girdle dystrophy. For many patients, misdiagnosis and disruption of their jobs and of social and family relationships are even more distressing than physical powerlessness. Therefore correct diagnosis including molecular genetic confirmation and proper treatment are mandatory. This article deals with the various hereditary muscle channelopthies such as congenital myasthenic syndromes, non-dystrophic myotonias, periodic paralyses, malignant hyperthermia, and central core disease. The responsible genes, the disease pathogenesis and the therapeutical options are described (Table 1).

Congenital myasthenic syndromes – not always congenital

Congenital myasthenic syndromes (CMS) are a heterogeneous group of inherited disorders with defective transmission of neuromuscular excitation resulting in muscle fatigue. Weakness is usually evident at birth or within the first year or two of life, and is characterized by feeding difficulties, ptosis, impaired eye movements, and delayed motor milestones. Strength sometimes improves during adolescence, and does not exhibit a progressive course. Reflexes are usually brisk and muscle wasting does not occur. CMS can lead to congenital ar-

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Table 1. Overview of hereditary muscle channelopathies.

Disease	Gene	Protein	Inheritance	Mutation	Therapy
Congenital myasthenic syndrome	*CHAT*	Ch-A-T^	recessive	loss	AChE-I, DAP
	COLQ	AChE	recessive		avoid AChE-I
	CHRNA-E	nAChR	domin./rec.	gain or loss	AChE-I, DAP°
	RAPSN	rapsyn	recessive	loss	AChE-I, DAP
	MUSK	MuSK	recessive		
	SCN4A	Nav1.4	recessive		
	DOK7	Dok-7	recessive		ephedrin, albuterol
Thomsen myotonia	*CLCN1*	ClC1	dominant	loss	propafenone, flecainide, acetazolamide
Becker myotonia			recessive	loss	
Potassium-aggravated myotonia	*SCN4A*	Nav1.4	dominant	gain	
Paramyotonia congenita					
Hyperkalemic periodic paralysis					HCT, albuterol
Normokalemic periodic paralysis				gain (ω-pore)	(K), CAI, AA
Hypokalemic periodic paralysis 2				gain (ω-pore)	K, CAI, AA
Hypokalemic periodic paralysis 1	*CACNA1S*	Cav1.1	dominant	gain (ω-pore)	K, CAI, AA
Thyrotoxic periodic paralysis*	*KCNJ18*	Kir2.18	dominant	loss	symptomatic
Andersen-Tawil syndrome	*KCNJ2*	Kir2.1	dominant	loss	CAI
Malignant hyperthermia*	*CACNA1S*	Cav1.1	dominant	gain	dantrolene (crisis)
	RYR1	RyR1	dominant	gain	dantrolene (crisis)
Central core disease			domin./rec.	gain or loss	exercise
Multiminicore disease			recessive	loss	exercise

° AChE-I and DAP to be avoided in the slow-channel syndrome, * Susceptibility, AChE-I = Acetylcholine-esterase inhibitor, DAP = 3,4-Diaminopyridine, HCT = Hydrochlorothiazide, K = Potassium, CAI = Carbo-anhydrase inhibitor, AA = Aldosterone antagonists, ^ Cholin-acetyl-transferase, Nav = voltage-gated sodium channel

throgryposis multiplex involving reduced fetal movement and multiple joint contractures in the neonate. Electromyography in CMS patients reveals a characteristic decrement of compound action potential (CMAP) amplitude on repetitive stimulation (3 Hz). The decrement usually starts at the second, rarely at the third CMAP, and ends at the 4th or 5th. After that, the decrement either improves or remains the same. The reduced transmission is usually improved by edrophonium. Single fibre recordings show an increased variability in the synaptic transmission time ("jitter") and transmission blocks.

Presynaptic, synaptic, and postsynaptic loss-of-function proteins

CMS result from defects in presynaptic, synaptic, and postsynaptic proteins. Presynaptic defects reduce acetylcholine release and resynthesis due to mutations in the choline acetyltransferase gene (CHAT). Synaptic CMS are caused by acetylcholinesterase (AChE) deficiency due to mutations in the COLQ gene encoding the collagenic tail subunit that mediates AChE insertion into the synaptic basal lamina. Postsynaptic CMS are caused by dominant or recessive mutations in the CHRNA1/B1/D/E genes for the nicotinic acetylcholine receptor subunits. Loss-of-function mutations, most frequently of CHRNE, lead to compensatory expression of fetal δ subunits yielding nicotinic acetylcholine receptor complexes which differ functionally from the adult type (2). Therefore proteins that anchor or stabilize these subunits are targets for CMS (3, 4). Mutations in the corresponding genes RAPSN, MUSK and DOK7 are similarly frequent and together as frequent as CHRNE mutations. DOK7 and COLQ mutations should be considered in patients presenting with proximal weakness and waddling gait and

inward rotation of the knees, even in the absence of symptoms suggesting a possible myasthenia (5). Late onset of symptoms may occur for RAPSN and DOK7 mutations and in the slow-channel syndrome.

"Kinetic" gain- and loss-of-function nicotinic acetylcholine receptor mutations

Rarely, postsynaptic CMS are caused by mutations at different sites and different functional domains that alter the kinetic channel properties. These kinetic mutations result in the slow- or fast-channel syndromes. The low-affinity, fast channel syndrome is caused by loss-of-function AChR subunit mutations that have similar effects as AChR deficiency. Mutations at different sites lead to fewer and shorter channel activations. In contrast to all above CMS, the slow-channel syndrome presents in childhood, adolescence or adult life with upper limb predominance and contractures, does not respond to acetyl-cholinesterase inhibitors, and is progressive. CMS patients with a slow-channel syndrome show increased synaptic response to Ach, i.e. characteristic repetitive discharges in response to a single supramaximal stimulus. The syndrome results from gain-of-function mutations in the ion-conducting pore M2. The leaky AChR exert an excitotoxic effect and cause endplate myopathy via focal caspase activation.

Myotonia – plasmalemmal hyperexcitability due to mutant Na^+ or Cl^- channels

Muscle stiffness, termed myotonia, ameliorates by exercise, the "warm-up phenomenon", and can be associated with transient weakness during strenuous muscle activity On the contrary, paradoxical myotonia (also called paramyotonia) worsens with cold and after exercise. Both myotonia and paramyotonia derive from uncontrolled repetitive 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 subsequently experience as muscle stiffness.

As in myasthenia gravis and the CMS, a CMAP decrement can occur at repetitive nerve stimulation at 3 Hz. In contrast to the CMS, it starts later and might be more pronounced (6, 7). It is caused by the increasing hypoexcitability of the muscle fiber membrane due to sustained membrane depolarization which is not improved by edrophonium. This decrement leads to a dramatic loss of isometric muscle strength during the first strong contractions after rest. With repeated contractions, CMAP amplitude and strength return. This transient weakness occurs in the Becker myotonia (Fig. 1) in which the stiffness is usually more pronounced than in the Thomsen type.

Chloride channel myotonias: Thomsen and Becker

Dominant Thomsen and recessive Becker myotonia are caused by missense and nonsense mutations in the homodimeric Cl^- channel encoded by *CLCN1*. Functionally, the dominant mutants exert a 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 resulting Cl^- currents is a shift of the activation threshold towards more positive membrane potentials almost out of the physiological range. As a consequence of this, the Cl^- conductance is drastically reduced in the vicinity of the resting membrane potential. The recessive mutants that do not functionally hinder the associated subunit supply the explanation of why two mutant alleles are required to reduce Cl^- conductance sufficiently for myotonia to develop in Becker myotonia.

Sodium channel myotonia and paramyotonia congenita (PMC)

In Na^+ channel myotonia and paramyotonia, there is a gating defect of the Na^+ channels destabilizing the inactivated state such that channel inactivation may be slowed or incomplete (8-10). This results in an increased tendency of the muscle fibers to depolarize which generates repetitive action potentials (myotonia). The mutant channels produce a dominant gain of function on the channel as well as on cell excitability (Fig. 2).

One hot spot for the PMC mutations is a special voltage-sensing transmembrane region that couples channel inactivation to channel activation; another hot spot is an intracellular protein loop containing the inactivation particle (Fig. 3). The potassium-aggravated myotonia (PAM) mutations are found in intracellular regions of the protein,

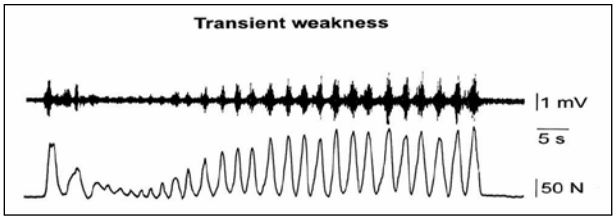

Figure 1. Transient weakness in a patient with recessive myotonia congenita.

Upper trace: surface EMG recorded over biceps brachii muscle. Lower trace: Concurrent isometric force generated by elbow flexors. Note ~5-6 s of diminished electrical and force activity followed by gradual recovery. N, Newton [from Lehmann-Horn et al., 2004 (1), mod.].

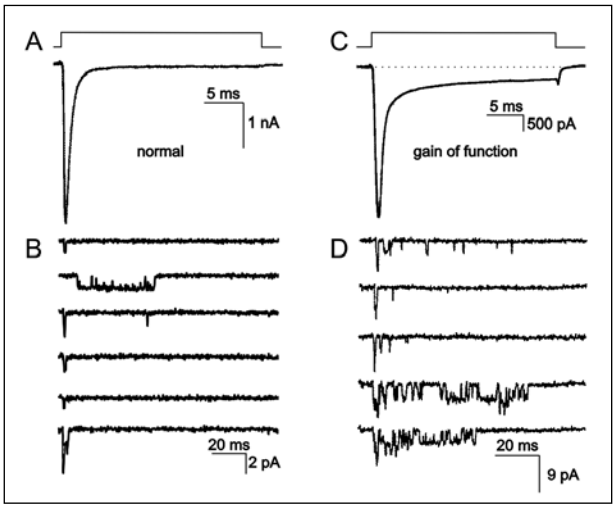

Figure 2. Currents through the central pore of normal and mutant Nav1.4 channels.

Macroscopic (A, C) and single-channel (B, D) sodium currents of normal and mutant Nav1.4 channels are shown. The currents were elicited by a depolarization step from a holding potential of -120 mV to +30 mV. Re-openings were more frequent for mutant channels, thereby leading to a small persistent current as verified by the tail current at the end of the pulse (C) [from Lehmann-Horn et al., 2004 (1), mod.].

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: 1) myotonia fluctuans where patients may not be aware of their disorder; 2) myotonia responsive to acetazolamide with a Thomsen-like clinical phenotype, and 3) myotonia permanens with continuous electrical myotonia leading to a generalized muscle hypertrophy including facial and neck muscles suggestive of facial dysmorphia (11-13). In all three types, body exertion or administration of depolarizing agents may result in a severe or even life-threatening myotonic crisis (1).

As PMC channels fail to inactivate completely in cold environment, the sodium inward current causes an intracellular sodium and water accumulation that can be visualized in vivo by 23Na- und 1H-MRI (14).

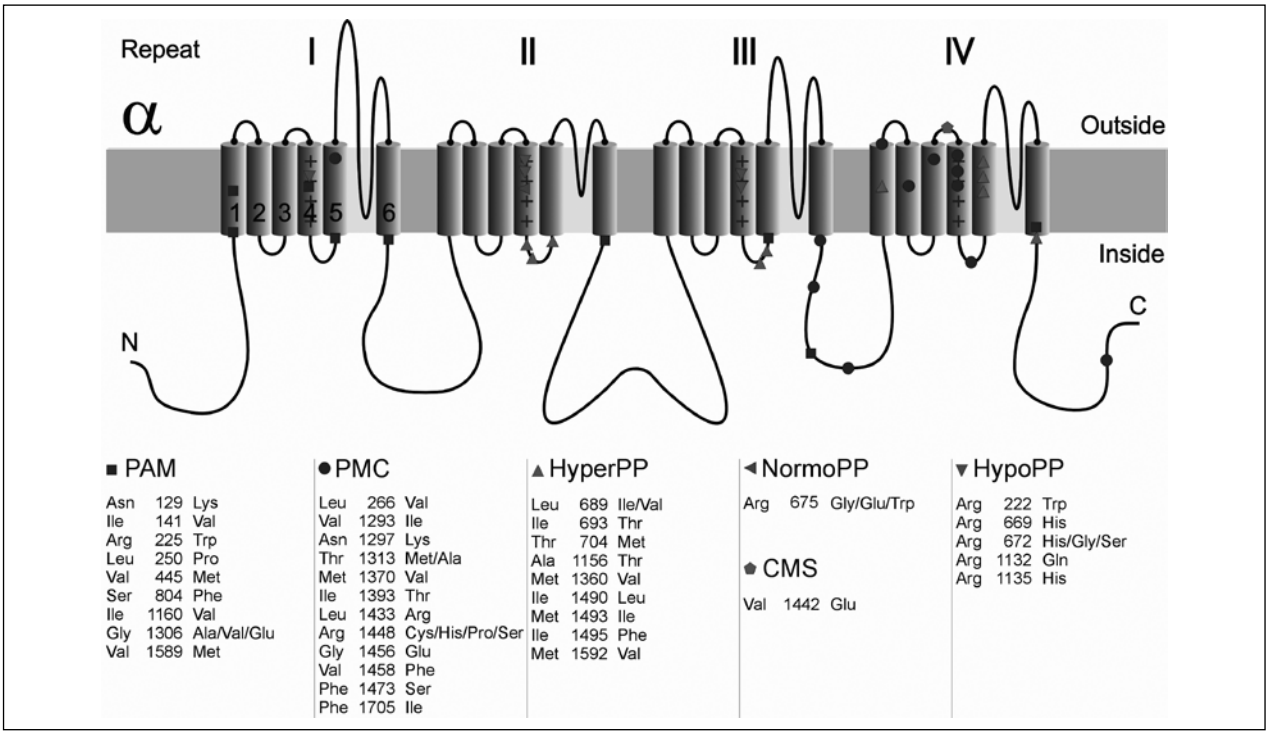

Figure 3. The voltage-gated sodium channel of skeletal muscle, $Na_V1.4$.

The alpha-subunit is composed of 4 highly homologous repeats (I-IV) each consisting of 6 transmembrane segments (S1-S6). When inserted in membrane, the 4 repeats of the protein fold to generate a central pore, whereby the S5-S6 loops form the ion-selective pore. The S4 segments contain positively charged residues conferring voltage dependence to the protein. Repeats are connected by intracellular loops; one of them, the III-IV linker, contains the inactivation particle of the channel. The sketch gives an overview of locations of known $Na_V1.4$-mutations [from Jurkat-Rott, et al. 2010 (32) mod.].

Periodic paralysis - plasmalemmal hypoexcitability due to mutant Na^+ or Ca^{2+} channels

Symptoms occur episodically with varying intervals of normal muscle function and excitation because ion channel defects are usually well-compensated and an additional trigger is often required for muscle inexcitability due to sustained membrane depolarization. This depolarization is responsible for the late CMAP decrement at repetitive nerve stimulation at 3 Hz (long-exercise test). It is not improved by edrophonium.

Three dominant episodic types of weakness with or without myotonia are distinguished by the serum K^+ level during the attacks of tetraplegia: hyper-, normo- and hypokalemic periodic paralysis (PP). Intake of K^+ and glucose has 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. Due to additional release of K^+ from hyperkalemic PP muscle and uptake of K^+ into hypokalemic PP muscle, dyskalemia can be that severe during a paralytic attack that cardiac complications arise. During an attack, death can also occur due to respiratory insufficiency.

Hyperkalemic periodic paralysis - Na^+ channel paralysis combined with myotonia

Most Nav1.4 mutations that cause hyperkalemic PP (HyperPP) are situated at inner parts of the transmembrane segments or in intracellular protein loops (Fig. 3) and affect structures that form the docking site for the fast inactivation particle. Thereby, they impair fast channel inactivation and lead to a persistent Na^+ current. At the beginning of an attack, the sustained inward current is associated with a mild membrane depolarization and leads to myotonia. The progressing attack is characterized by membrane inexcitability and muscle weakness since the penetrated Na^+ ions go along with a more severe sustained membrane depolarization that inactivates most Na^+ channels. Dependent on the location of the underlying mutation, symptoms typical of HyperPP, K^+-aggravated myotonia, and paramyotonia congenita can overlap in a given patient (15). As in PMC, HyperPP channels fail to inactivate completely, and the sodium inward current causes an intracellular sodium and water accumulation that can be visualized in vivo by 23Na- und 1H-MRI (14).

Hypokalemic periodic paralysis – caused by Na^+ and Ca^{2+} channel outer S4 mutations

Hypokalemic PP (HypoPP) differs from the hyperkalemic form in the sense that a spontaneous attack is associated with hypokalemia, potassium is a remedy, whereas carbohydrate- and sodium-rich food triggers an attack. In general, the attacks last longer and are more severe. Usually, the patients are weakest during the second half of the night and in the morning, and become stronger as the day goes by.

HypoPP is caused by mutations in two voltage-gated cation channels in skeletal muscle Cav1.1 (HypoPP-1) and Nav1.4 (HypoPP-2) (Fig. 3) (16). Almost all mutations neutralize a positively charged amino acid in one of the outermost arginines or lysines of a voltage sensor. The Nav1.4 mutations are situated in the voltage sensors of repeats I, II and III. The electrophysiological characterization of the gating defects induced by these mutations revealed a loss of channel function, which does not explain the phenotype. By expressing HypoPP mutations in *Xenopus* oocytes, a cation leak was discovered that showed the typical characteristics found for the ω-current in Shaker K+-channels (17-19). The ω-current, so called to differentiate it from the (ω-)current through the ion-conducting pore, is a hyperpolarization-activated current of monovalent cations that is though to flow through the S4 gating pore (Fig. 4). The ω-current counteracts the rectifying K^+ currents and therefore depolarizes and destabilizes the resting membrane potential so that the fraction of depolarized, inexcitable fibers is increased (20). In vivo, the muscles from these patients exhibited an intracellular sodium accumulation and edema (21).

As muscle fibers with a severe voltage sensor mutation are depolarized not only during hypokalemia but also at potassium levels in the normal range, this membrane leak might not only explain episodes of weakness, but interictal (permanent) weakness as well. The permanent weakness associated with a fatty replacement myopathy is very frequently found in patients harboring DIV mutations in the calcium channel, i.e. Cav1.1 R1239H (21).

Normokalemic periodic paralysis – caused by Na^+ channel inner S4 mutations

The term normokalemic PP was originally given to a variant described in the 1960s. The disorder resembled hyperkalemic PP in many aspects; the only real differences were the lack of increase in the concentration of serum potassium even during serious attacks, and the lack of a beneficial effect of glucose administration (1). Recently, a potassium-sensitive type of periodic paralysis with normokalemia and episodes of weakness reminiscent of those in both hyperkalemic (initiation of an attack by potassium) and hypokalamic forms (duration of attacks) was reported (22). This phenotype, is caused by SCN4A mutations at deeper locations of the voltage sensor of domain II at codon 675. Functionally, R675 mutations generate an ω-current with a reversed voltage dependence compared

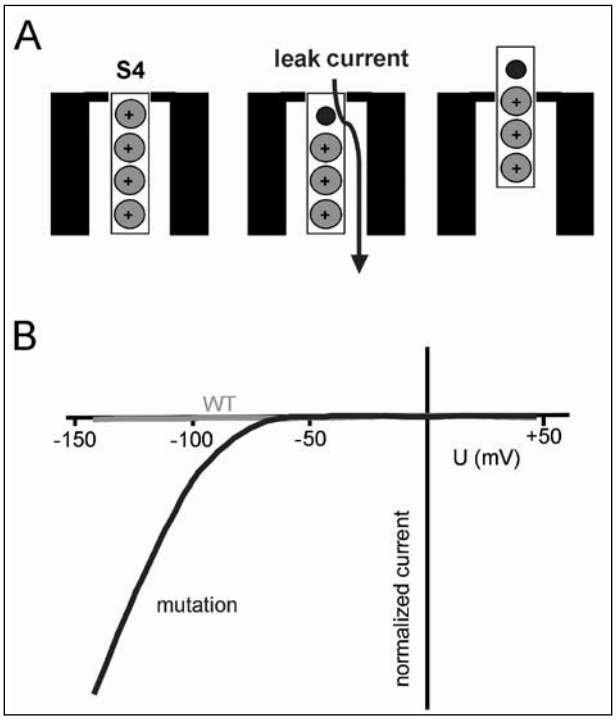

Figure 4. Leak currents through mutant voltage sensors.
(A) A replacement of the outermost arginine (left) by a smaller amino acid e.g. glycine (center), opens a conductive pathway at hyperpolarized potentials, resulting in an inward cation current (arrow). At depolarized potentials at which the S4 segment moves outward (right), the conductive pathway is closed and the cation current ceases. (B) Schematic of cation currents through sodium channels carrying charge-neutralizing substitutions in S4 voltage sensors. Note the large inward current in the hyperpolarized potential range corresponding to the resting state of the leaky S4 voltage sensor [from Jurkat-Rott, et al. 2010 (32) mod.].

to mutations causing HypoPP-2, since this site is exposed to the extracellular space at stronger depolarizations (23). The diagnostics for NormoPP are as described for the two more common forms of the disease. The therapy consists of avoidance of both hypokalemia and hyperkalemia and the administration of acetazolamide.

K^+ channel periodic paralysis with cardiac arrhythmia

Patients with Andersen-Tawil syndrome may experience a life-threatening ventricular arrhythmia independent of their PP is the primary cardiac manifestation. The syndrome is characterized by the highly variable clinical triad of dyskalemic PP, ventricular ectopy, and potential dysmorphic features (24). The paralytic attack may be hyperkalemic or hypokalemic and accordingly, the response to oral K^+ is unpredictable. Mutations of the Kir2.1 K^+ channel, an inward rectifier expressed in skeletal and cardiac muscle, are causative of the disorder. Kir2.1 channels are essential for maintaining the highly negative resting membrane potential of muscle fibers and accelerating the repolarization phase of the cardiac action potential. The mutations mediate loss of channel function by haploinsufficiency or by dominant-negative effects on the wildtype allele and may lead to long-lasting depolarization, fiber membrane inexcitability and paralysis.

Muscle channelopathies due to an altered excitation-contraction coupling

Muscle contractures, i.e. electrically silent contractions due to intracellular Ca^{2+} exceeding the mechanical threshold, as well as flaccid weakness are characteristic features of disturbed muscle excitation-contraction coupling. Two allelic forms are well studied: malignant hyperthermia (MH) and central core disease (CCD).

Malignant hyperthermia

Susceptibility to MH is an autosomal dominant predisposition to respond abnormally when exposed to volatile anesthetics, depolarizing muscle relaxants or extreme physical activity in hot environments. During exposure to triggering agents, a pathologically high increase in myoplasmic Ca^{2+} concentration leads to increased muscle metabolism and heat production resulting in muscle contractures, hyperthermia associated with metabolic acidosis, hyperkalemia, and hypoxia. The metabolic alterations usually progress rapidly and without immediate treatment, up to 70% of the patients die. Early administration of dantrolene, an inhibitor of Ca^{2+} release from the sarcoplasmic reticulum (SR) has successfully aborted numerous fulminant crises and has reduced the mortality rate to less than 10%.

In most families, mutations can be found in the gene encoding the skeletal muscle ryanodine receptor, RyR1. This Ca^{2+} channel is not voltage-dependent on its own, but exists under the control of Cav1.1. MHS mutations are usually situated in the cytosolic part of the protein and show gain-of-function effects: they increase RYR1 sensitivity to caffeine and other activators as shown in functional tests of both excised muscle, isolated native proteins, and ryanodine receptors expressed in muscle and non-muscle cells. For another MH locus on chromosome 1q31-32, an R1086H disease-causing mutation was identified in the skeletal muscle L-type calcium channel alpha1 subunit. The mutation is located in an intracellular loop of the protein whose functional significance for EC coupling is under debate. Although mutations in the same gene cause hypokalemic periodic paralysis type 1 this disorder is not thought to be associated to MH susceptibility.

Central core disease (CCD) and multiminicore disease (MmD)

CCD is a mainly dominant congenital myopathy. Although it is genetically heterogeneous, most patients harbour a *RYR1* mutation (25). It is clinically characterized by muscle hypotrophy and weakness and a floppy infant syndrome, often alongside other skeletal abnormalities such as hip displacement and scoliosis. Pathognomonic is the abundance of central cores devoid of oxidative enzyme activity along the predominant type 1 muscle fibers. Most RyR1 mutations are situated in the SR-luminal region. Some decrease the open probability of the RyR1 channel so that it loses the ability to release Ca^{2+} in response to the conformational DHPR alteration that is induced by depolarization of the plasma membrane.[26] However, RyR1 retains the ability to influence the open probability of the DHPR. Other mutations increase the open probability of the RyR1 channel, leading to depleted SR Ca^{2+} stores and weakness.

MmD is recessively inherited and genetically heterogeneous (27). The moderate form with generalized muscle weakness predominantly of the pelvic girdle, hand involvement, amyotrophy, and hyperlaxity is often associated with RYR1 mutations. In contrast to CCD, the cores are usually multiple, poorly defined and do not extend along the whole fiber.

Medication of muscle channelopathies

In many CMS, acetylcholineesterase inhibitors (AChE-I) and 3,4-diaminopyridine (3,4-DAP) are effective on the short- and long-term. In the AChE-deficiency and the slow-channel syndrome, inhibitors have to be avoided. In the latter, fluoxetine is very effective. In CMS caused by *DOK7* mutations, edrophonium might be successful, whereas AChE-I are not effective on the long-term. However these patients respond to ephedrine and albuterol.

The aim of drug therapy in myotonia and paramyotonia is to reduce the unvoluntary action potential bursts without blocking voluntary high-frequency muscle stimulation. Local anesthetics and anti-arrhythmic drugs of class IB or IC effectively relieve stiffness in chloride and sodium channel myotonia and prevent weakness occurring in PMC with cooling. Agents such as mexiletine (unfortunately taken from the market because of profit shrinkage) and other lidocaine analogs and the IC antiarrhythmic drugs flecainide and propafenone, prevent repetitive firing of action potentials due to their "use dependence", a dependence of the depth of block on the frequency of action potentials. The degree of use dependence varies with the structure (charge and hydrophobicity) of the drug. Beyond this "unspecific" antimyotonic effect, the agents seem to be more effective on certain mutant sodium channels than on normal channels. Particularly mutant sodium channels that exhibit an enhanced closed-state inactivation are sensitive which suggests potential for mutation-specific treatment (28, 29). Recently relief from episodic weakness with pyridostigmine was reported for a PMC family (30). However it should be kept in mind that pyridostigmine can exacerbate myotonia.

Unfortunately the spontaneous and potassium-induced attacks of weakness typical for HyperPP and also occurring in some PMC patients are not improved by lidocaine analogs or antiarrhythmic drugs. However diuretics such as hydrochlorothiazide and acetazolamide can decrease frequency and severity of paralytic episodes, probably by lowering serum potassium and perhaps by shifting the pH to lower values.

In HypoPP, acute weakness spells can be treated by potassium and be prevented by certain carbonic anhydrase inhibitors, aldosterone antagonists, and potassium-sparing diuretics. Serum potassium levels in the high normal range help reduce the paradoxical membrane depolarization and therefore shift the resting potential to more normal values. Acetazolamide also lowers intracellular sodium accumulation in these patients addressing both pathogenetic factors in HypoPP: depolarization and sodium accumulation (21). The repolarizing effect of acetazolamide may be explained at least partially by opening of big conductance potassium channels (31).

During a malignant hyperthermia crisis, sufficient amounts of the antidote dantrolene have to be administered intravenously in addition to symptomatic treatment such as the immediate stop of the triggering agents. In CCD, muscle strength can be improved by exercise (unpublished observation).

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