

## Chapter 3

# Myotonic disorders

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### 3.1. A glossary of myotonia

By definition, *myotonia* is a feature of muscle fiber dysfunction. Proof of this can be achieved with curare. This differentiates the myotonia from *neuromyotonia*, which is caused by spontaneous motor unit activity due to hyperexcitability of the terminal motor nerve branches. Myotonia is characterized by an involuntary muscle tension that is caused by a lowered electrical threshold and action potentials which repetitively fire because of a hyperexcitability of the muscle fiber membrane. Usually myotonia does not occur spontaneously but depends on the patient's past activity. Myotonia is most prominent in muscles that are strenuously activated for a few seconds after they have rested for >10 minutes. Under these conditions, muscle relaxation is severely slowed due to the involuntary after-activity. If the myotonia is severe, *transient weakness* can occur. The myotonia decreases with continued activity, a phenomenon called *warm-up*. Also the weakness, if present at all, resolves. On the contrary, *paradoxical myotonia* or *paramyotonia* worsens with exercise in the cold. Paradoxical myotonia of the eyelid muscles may also occur in the warmth; it is indicative of sodium-channel myotonia. The *lid lag phenomenon* is positive when the white sclera between the iris and the lagging upper lid are visible after a sudden downward gaze following a several-second-lasting upward gaze. *Percussion myotonia* is the reaction to a blow with the reflex hammer characterized by an indentation along the muscle fibers. In contrast, *myoedema* shows a transverse bulging of the percussed muscle. Myotonia may or may not be aggravated by ingestion of potassium. The former is called *potassium-aggravated myotonia*, a symptom that is indicative of *sodium-channel myotonia*, a syndrome caused by a sodium-channel mutation. On electromyographic (EMG) examination, myotonic

muscles exhibit *myotonic runs*, i.e., action potentials characterized by a modulation of frequency and amplitude. In mild cases myotonia may not be evident on clinical examination, yet EMG may reveal the typical myotonic bursts. This is termed *latent myotonia*.

### 3.2. Membrane excitability

Voltage-gated ion channels regulate the membrane excitability of muscle and nerve. It is therefore not surprising that mutant channels can cause diseases of these tissues, so-called channelopathies. Muscle channelopathies are characterized by either transient membrane hyperexcitability (i.e., myotonia) or hypoexcitability (i.e., paralysis) or both (Jurkat-Rott and Lehmann-Horn, 2005a). Loss-of-function mutations of the inhibitory chloride channel as well as gain-of-function mutations of the excitatory sodium channel cause membrane hyperexcitability such as in the classical congenital myotonias and in potassium-aggravated myotonia. The inward current through the mutant sodium channels is associated with a sustained membrane depolarization that can inactivate the remaining sodium channels and render the membrane unexcitable. This happens in paramyotonia in the cold and in hyperkalemic periodic paralysis at elevated serum potassium levels.

### 3.3. Chloride-channel myotonias

#### 3.3.1. Thomsen and Becker myotonias

The two classical forms of myotonia are distinguished by their mode of inheritance and the severity of their clinical features: the relatively mild dominant myotonia congenita (or Thomsen disease, MIM 160800) and the more severe recessive myotonia congenita (or Becker

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myotonia, MIM 255700). Both disorders progress slowly during childhood and adolescence, neither form present as muscular dystrophy, and both forms are caused by mutations in the gene, *CLCN1*, coding for the voltage-gated chloride channel of the plasma membrane (Koch et al., 1992; George et al., 1993). For this reason, they are also referred to as chloride-channel myotonias.

The prevalence of Thomsen disease has turned out to be much lower than thought in the premolecular era (1:23 000; Becker, 1977); it is now estimated at ~1:400 000. Families with an apparent dominant trait were later found to have Becker myotonia with pseudodominant inheritance and others were identified as carriers of a sodium-channel mutation. Conversely, the prevalence of Becker myotonia is likely higher than Becker's original estimate of 1:50 000 (Becker, 1977).

Generally, the stiffness in patients with Thomsen and Becker myotonia is initiated by a forceful muscle contraction, particularly after rest for at least 10 minutes. This does not necessarily pertain to the first contraction which may be relatively unimpeded. The myotonic muscle stiffness becomes increasingly obvious following a second and third short but forceful contraction. Further contractions typically dampen the myotonia gradually. This "warm-up" phenomenon then lasts for several minutes. Its pathomechanism remains unclear.

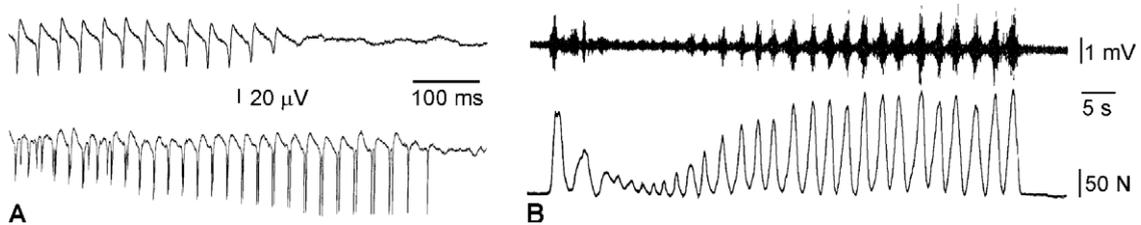
Upon examination, patients with Thomsen myotonia may present with hypertrophic muscles and an athletic appearance. Their muscle strength is normal or even greater than normal and they can be quite successful in sports that require strength more than speed. Percussion myotonia and lid lag are usually present and, in some patients, the lid muscle myotonia results in blepharospasm after forceful eye closure. The muscle stretch reflexes are normal and muscle pain is usually not present. The myotonic signs persist throughout life.

The clinical picture of Becker myotonia resembles that of Thomsen disease. A few special points are worth mentioning. In many patients with Becker myotonia, the stiffness is not manifest until the age of 10–14 years or even later, but in a few it is already obvious at the age of 2–3 years. The severity of the myotonia may slowly increase for a number of years, but usually not after the age of 25–30. The myotonia is more severe than in Thomsen disease. Thus, patients with Becker myotonia are more handicapped in daily life, and especially by myotonic stiffness of the leg muscles that causes gait problems. Situations requiring rapid motor control may provoke severe generalized stiffness causing these patients to fall to the ground without being able to protect themselves, and to be injured or rendered unconscious through head injury. This has previously led to the misdiagnosis of epilepsy, prompting the use of antiepileptic drugs which improved the myotonia.

Muscle shortening due to continuous contractions may limit dorsiflexion of the wrist or foot. Severely affected patients with Becker myotonia tend to toe-walk and develop a compensatory lordosis. The leg and gluteal muscles are often markedly hypertrophic. In some patients, especially older ones, the neck, shoulder and arm muscles appear poorly developed resulting in a characteristic disproportionate figure. Also very disabling is a peculiar transient weakness affecting especially the hand and arm muscles (Deymeer et al., 1998). This lasts only a few seconds following initial contraction and may be interpreted as clumsiness by the affected individual. Patients with severe Becker myotonia are limited in their choice of occupation and are unsuited for military service. A few patients with Becker myotonia show permanent weakness in some muscle groups, distal muscle atrophy, and unusually high serum creatine kinase (CK) levels, making the differentiation from myotonic dystrophies difficult. Life expectancy is normal.

### 3.3.1.1. EMG

The electrophysiological correlate of myotonia, regardless of the type of channel affected, is involuntary repetitive firing of muscle fiber action potentials. The impressive electrical activity following a voluntary contraction is too painful to monitor. Instead, the EMG needle is usually inserted into the resting muscle. Needle insertion itself elicits myotonic bursts. In patients with Thomsen and Becker myotonia, the myotonic bursts can be observed in all routinely examined skeletal muscles. Typically, short bursts of action potentials appear as triphasic spikes or as positive sharp waves with amplitude and frequency modulation. Most frequent are short bursts characterized by a rising frequency and a falling spike amplitude (Fig. 3.1). An often mentioned, but actually rare, pattern is a short discharge characterized first by an increase in frequency and decrease in amplitude and then by a decrease in frequency and increase in amplitude. It resembles the sound of a dive-bomber when recorded in the acoustic EMG. In a few recessive myotonia congenita families, latent myotonia can be demonstrated in the heterozygous parents of affected offspring; that is, repetitive action potentials are seen on EMG without clinical features of myotonia (Deymeer et al., 1999). Motor unit potentials are usually normal. Myopathic changes such as multiphasic or low-amplitude potentials can be observed in the rare patients with Becker myotonia who have permanent weakness (Nagamitsu et al., 2000). Compound muscle action potential (CMAP) amplitudes are reduced during transient weakness and upon repetitive stimulation (Fournier et al., 2004). Consistent with the less



**Fig. 3.1.** Myotonic runs and transient weakness in a patient with Becker myotonia. A. The two EMG traces show typical myotonic runs of short duration, waxing frequency and waning amplitude. The final high-frequency phase of some runs causes a tetanic contraction of the spiking muscle fiber which induces another discharge in a surrounding fiber. B. Surface EMG of biceps brachii muscle (upper trace) and voluntary isometric force (in Newton) of the forearm flexors (lower trace) show a pattern characteristic for transient weakness. Modified after Ricker et al. (1978b).

pronounced transient weakness in patients with Thomsen than those with Becker myotonia, a higher stimulation frequency is necessary to induce the same effect (Deymeer et al., 1998). Multichannel surface EMG reveals a gradually developing decrease in peak-to-peak amplitude of the motor unit action potentials from end-plate towards tendon in parallel with the force decline. This deteriorating membrane function leads transiently to a complete intramuscular conduction block (Drost et al., 2001).

### 3.3.1.2. Microscopy

Muscle biopsy, which is not part of the diagnostic process, is usually normal. In some, slight myopathic changes with increased occurrence of central nuclei and pathological variation of fiber diameter may be found. Muscle fiber hypertrophy, especially of type 2A fibers, and fiber atrophy may be present. Finally, there may be reduction or complete absence of type 2B fibers (Jurkat-Rott et al., 2002).

### 3.3.1.3. Molecular genetics and pathogenesis

The causative gene for dominant Thomsen and recessive Becker myotonia is *CLCN1* on chromosome 7q encoding the voltage-gated chloride channel of the skeletal muscle fiber membrane. The chloride channel protein, CIC-1, forms homodimeric double-barrel complexes (Mindell et al., 2001; Dutzler et al., 2002) with two ion-conducting pores (Saviane et al., 1999; for review see Fahlke, 2001). Over 70 CIC-1 mutations have been identified (Fig. 3.2; Koch et al., 1992; George et al., 1993; Heine et al., 1994; Lorenz et al., 1994; Lehmann-Horn et al., 1995; Koty et al., 1996; Mailänder et al., 1996; Sangiuolo et al., 1998; Brugnoli et al., 1999; Sasaki et al., 1999, 2001; Wu et al., 2002; reviewed in Pusch, 2002), making genetic studies quite arduous. While nonsense and splicing mutations usually lead to the recessive phenotype, missense mutations are found in both Thomsen and Becker myotonia. After the first description as dominant, several mutations — all of which were functionally

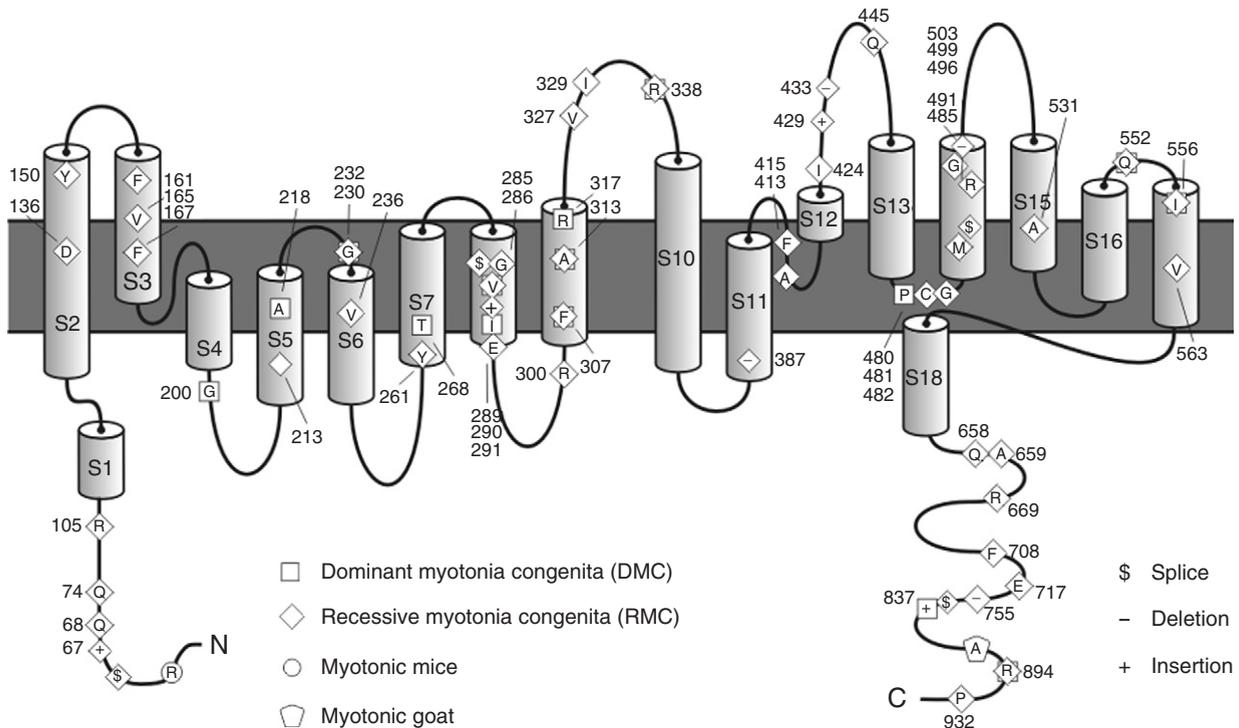
expressed and shown to have a “dominant-negative effect” on coexpressed wildtype (Meyer-Kleine et al., 1995; Pusch et al., 1995; Kubisch et al., 1998; Zhang et al., 2000) — were also found in families with a recessive mode of inheritance or in a homozygous state (George et al., 1994; Meyer-Kleine et al., 1995; Zhang et al., 1996; Sloan-Brown and George, 1997; Esteban et al., 1998; Plassart-Schiess et al., 1998). According to our own data, some seemingly dominant pedigrees can be explained by pseudodominant transmission by multiple recessive mutations (Mao et al., unpublished data). Hitherto, only three families with pseudodominant transmission have been described (Papponen et al., 1999; Sun et al., 2001). If mutation screening is negative, linkage analysis that includes a sufficient number of informative additional family members may confirm the diagnosis.

### 3.3.2. Myotonia associated with muscle dystrophies

Myotonic dystrophy (DM) is a progressive multisystemic disease with muscle wasting, myotonia, subcapsular cataracts, cardiac conduction defects, gonadal atrophy, mild deafness and cognitive deficits. There are two clinically distinguished types: DM1 with the classical phenotype and a milder DM2 type with a more proximal pattern of weakness.

#### 3.3.2.1. Myotonic dystrophy type 1

Myotonic dystrophy type 1 (DM1; MIM 160900) is an autosomal dominant multiorgan disease and the most common inherited muscle disorder in adults. Myotonia is only one of the many symptoms of this progressive disease, the most severe symptom being muscle weakness that begins in the distal limb and cranial muscles (*myopathic face*). Subcapsular cataracts with a characteristic iridescent appearance, gonadal atrophy, cardiac conduction abnormalities, mild deafness and cognitive deficits are evident to varying degrees. The mutation of DM1 is an expansion of an unstable CTG trinucleotide repeat in



**Fig. 3.2.** Membrane topology of the chloride channel. The model shows the skeletal muscle chloride channel monomer, CIC-1. The functional channel is a homodimer encoded by the *CLCN1* gene. The different symbols used for the known mutations leading to either dominant or recessive myotonia in man, mouse and goat are explained on the bottom. Conventional one-letter abbreviations are used for replaced amino acids.

the 3' untranslated region of the myotonic dystrophy protein kinase (*DMPK*) gene on chromosome 19q13.3 (for review see [Conne et al., 2000](#)).

A phenotype not found in Thomsen or Becker myotonia is a severe congenital form of DM1 characterized by generalized muscle weakness at birth (floppy infant) and retarded motor and mental development. Myotonia is absent in infancy. The diagnosis is readily established by detecting signs of dystrophy in the patient's mother and by genetic analysis that reveals a large CTG expansion in the infant.

In adults with myotonic dystrophy, myotonic EMG activity is less striking than in the non-dystrophic myotonias and is unevenly distributed between muscles. Distal muscles of the upper extremity and orbicularis oris muscles show the highest incidence of electrical myotonia. Long-lasting discharges of 2–30 s duration with falling or unchanging frequency and amplitude occur more often than the typical short myotonic runs typically observed in non-dystrophic myotonia. The maximal frequency of the discharges is 40–60 Hz and thus lower than in chloride-channel myotonia. Positive sharp waves and complex repetitive discharges are also very common.

### 3.3.2.2. Myotonic dystrophy type 2 or PROMM

A second dominant multisystemic myotonic disorder, similar to classical myotonic dystrophy but with no *DMPK* gene involvement, was originally described as proximal myotonic myopathy or PROMM ([Ricker et al., 1994a](#)). Since some patients exhibited distal muscle weakness and dystrophy ([Ranum et al., 1998](#)), the disease was later renamed myotonic dystrophy type 2, a broader category that also includes PROMM (DM2; OMIM 602668). The disease locus for DM2 is on chromosome 3q ([Ranum et al., 1998](#); [Ricker et al., 1999](#)). The mutation is an expansion of an unstable CCTG tetranucleotide repeat in intron 1 of the *ZNF9* gene coding for zinc finger protein 9. Parallels between mutations in DM1 and DM2 indicate that repeat expansions in RNA can be pathogenic and cause multisystemic deficits in both diseases ([Liquori et al., 2001](#)).

In most patients, DM2 progresses very slowly, with weakness developing typically after the age of 40. Some patients have troublesome, sometimes disabling, muscle pains, especially in the thighs. The pain is not related to myotonic stiffness and is most apparent at night. In other patients the early onset of cataract may be the first recognized manifestation of the disorder. The cataract

is posterior capsular and, during early stages, iridescent as in myotonic dystrophy. Many patients first complain of intermittent stiffness. When this is present, it is typically focal, involving one thigh or one hand. The movements are jerky and stepwise, especially in the thumb and the index finger and show the warm-up phenomenon. Because the severity of the myotonia is variable and the disorder is usually mild in the initial stages, it is not unusual for the signs of myotonia to elude clinical detection. Electromyographic investigation usually reveals myotonic discharges, even in those patients without obvious clinical myotonia. These myotonic discharges are often scarce and difficult to detect. A myopathic EMG pattern may be detectable in the most affected muscles. For all the myotonias discussed above, genetic analysis is available to confirm the diagnosis.

### 3.3.3. Animal models

About 30 years after the first description of myotonia in man, White and Plaskett (1904) described a breed of “fainting” goats raised in Tennessee, USA. The animals tended to have attacks of extreme muscle stiffness when attempting a quick forceful motion, so that they often fell to the ground for 5–20 seconds with extended neck and limbs. Clark et al. (1939) were the first to refer to the disease as “a form of congenital myotonia in goats”. Much later, susceptibility to malignant hyperthermia was excluded (Newberg et al., 1983).

In the late 1970s, two spontaneous mouse mutations were detected, one in the A2G strain in London, UK, the other in the SWR/J strain in Bar Harbor/Maine, USA. The behavioral abnormalities of the affected animals were very similar, and in both mutants the sign was transmitted as an autosomal recessive trait. The British scientists were struck by the observation that from days 10–12 onwards, the affected animals had difficulty in righting themselves when placed supine and therefore called the mutation *adr* for “arrested development of righting response”. The Americans observed that shaking the cage provoked sustained extension of an animal’s hind limbs, and since electrical myotonia was recorded in the EMG from the stiff muscles, this strain was called *mto* for “myotonic”. As far as the phenotype is concerned, the two models of myotonia are virtually indistinguishable.

### 3.3.4. Molecular pathogenesis of the chloride-channel myotonias

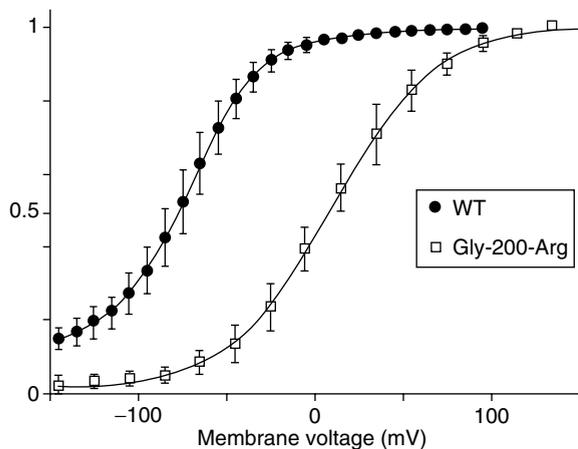
In contrast to most cells, the chloride conductance of muscle fibers is very high, making up ~80% of the total membrane conductance at rest. This high chloride conductance stabilizes the resting membrane potential and

inhibits potential deviations. Therefore, a decrease of the chloride conductance should cause membrane hyperexcitability. This hypothesis has been proven by experiments on myotonic goat muscle fibers which showed no, or a strikingly reduced, chloride conductance (Bryant, 1969) and later confirmed for human myotonia congenita (Lipicky et al., 1971; Rudel et al., 1988). The myotonic goat did not play a role in the identification of the gene defect responsible for the reduced chloride conductance. The mutation in the homologous goat gene was detected (Beck et al., 1996) long after *CLCN1* was localized and cloned for mouse (Steinmeyer et al., 1991) and man (Koch et al., 1992). The mutation in the goat gene predicts an Ala-885-Pro substitution in the C terminus of the chloride channel protein (Fig. 3.2) that right-shifts the activation curve of the chloride current, much like the dominant mutations do in man.

As in the myotonic goat and in human myotonia congenita, the reason for the abnormal excitability in the myotonic mice is a reduced chloride conductance. Homology cloning of the chloride channel gene expressed in skeletal muscle of the *adr* mouse identified an insertion that destroys the gene’s coding potential for several membrane spanning domains (Steinmeyer et al., 1991). Later, it was found that the *mto* allele carries a stop codon, leading to a truncation of the N-terminus (Fig. 3.2).

In heterologous expression systems, the most common feature of mutant human chloride channels 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 chloride conductance is drastically reduced in the crucial vicinity of the resting membrane potential (Fig. 3.3). This leads to a reduced membrane conductance for chloride and decreases the stability of the membrane potential, especially following an action potential. Coexpression studies showed that dominant mutations exert a dominant-negative effect on the dimeric channel complex. This means that mutant/mutant complexes, i.e., 25%, and mutant/wildtype, i.e., 50% of the complexes, are malfunctioning. The resulting chloride conductance is reduced to 25% (wildtype/wildtype), so that clinical myotonia develops (Palade and Barchi, 1977). In contrast, the gene product altered by a nonsense mutation is unstable so that neither mutant/mutant nor mutant/wildtype complexes are formed. The wildtype/wildtype complexes establish 50% of the normal chloride conductance in the heterozygous mutation carriers, a value that is sufficient for an almost stable membrane potential. Therefore Becker myotonia requires mutations on both alleles.

The pathogenesis of myotonia in the myotonic dystrophies is not fully understood. In DM1, the ion channel



**Fig. 3.3.** Voltage dependence of open probability of a dominant CIC-1 mutation. Behavior of human skeletal muscle CIC-1 channels expressed in a mammalian cell line. Compared are the relative open probabilities of normal (WT) and mutant (Gly-200-Arg) channels, the latter causing Thomsen myotonia. Note that the open probability of the mutant channel is strikingly reduced in the physiological potential range. All mutations that cause such a voltage shift have dominant effects. Adapted from [Wagner et al. \(1998\)](#).

disturbance likely stems from increased or alternative splicing leading to non-functional chloride channel gene products. The most abundantly occurring variants are retention of intron 2 and insertion of two accessory exons 6b and 7a ([Charlet et al., 2002](#); [Mankodi et al., 2002](#)). Two splice variants, leading to a truncated protein of 283 amino acids, exerted a dominant-negative effect on coexpressed wildtype CIC1 channel in *Xenopus* oocytes ([Berg et al., 2004](#)). In DM2, exclusion of exons 6 and 7 is the most abundant variant (S-F Ursu et al., unpublished data). The truncated protein of 236 amino acids, did not exert a truly dominant-negative effect on co-expressed wildtype CIC1, but only a slightly suppressive effect. Confocal laser microscopy suggested that a CIC1<sub>236X</sub> interaction with CIC1 may occur, though not regularly. In agreement with this observation, nonsense mutations of CIC1 resulting in early truncations nearby, such as fs231X, fs258X, or fs289X, are all inherited in a recessive manner.

### 3.4. Sodium-channel myotonias

Three dominantly inherited skeletal muscle sodium-channel myotonias have been delineated in humans on the basis of their clinical phenotype: potassium-aggravated myotonia (PAM, MIM 608390); paramyotonia congenita (MIM 168300), and hyperkalemic periodic paralysis (HyperPP, MIM 170500; [Jurkat-Rott and Lehmann-Horn, 2005b](#)). Two other skeletal muscle sodium channelopathies, hypokalemic periodic

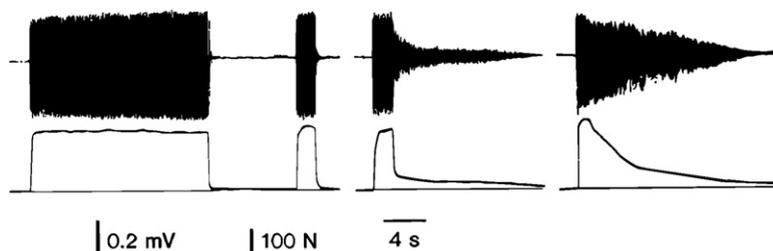
paralysis (HypoPP type 2; [Jurkat-Rott et al., 2000](#)) and a subtype of the congenital myasthenic syndromes ([Tsujino et al., 2003](#)) are not associated with myotonia but with hypoexcitability due to a reduced channel function. The acronyms for the periodic paralyses follow the recommendation of an international expert consortium ([Lehmann-Horn et al., 1993](#)). The periodic paralyses are discussed in detail in Chapter 4 and therefore mentioned here only as far as needed for better comprehension.

#### 3.4.1. Potassium-aggravated myotonias

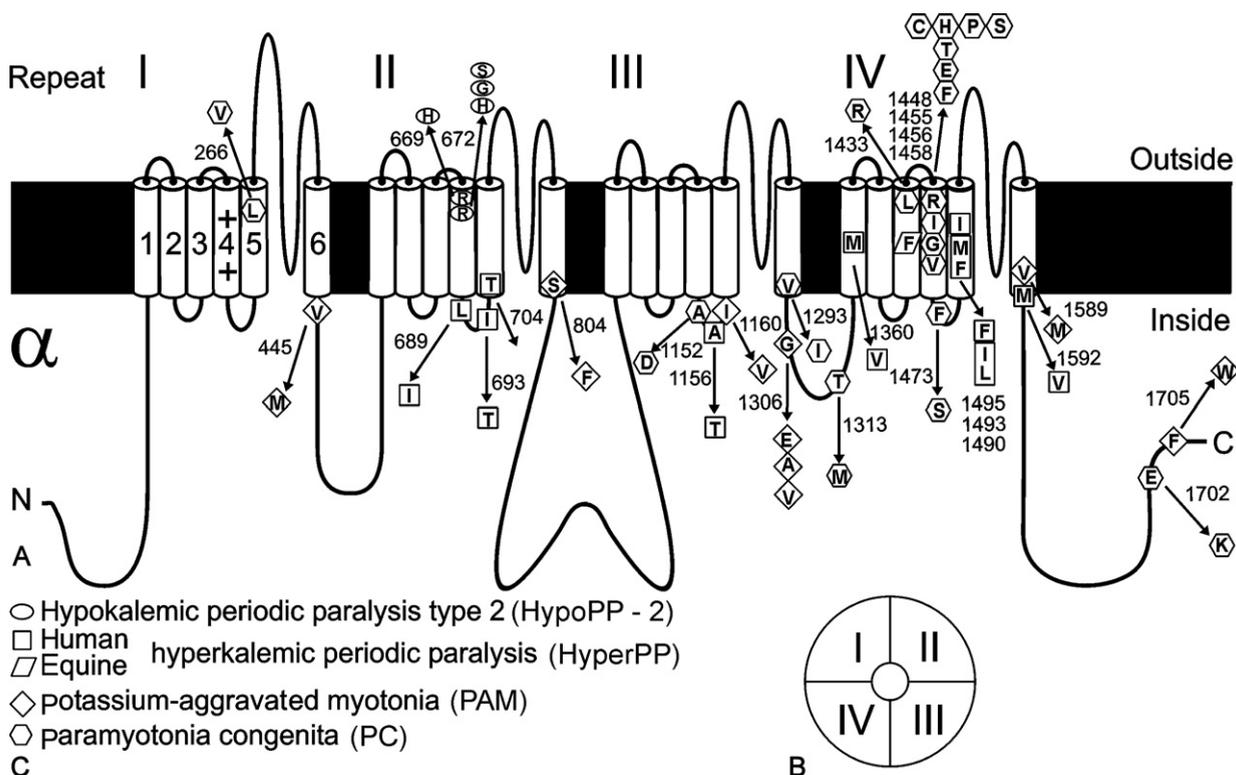
In 1994, the term potassium-aggravated myotonia was coined by [Mitrovic et al. \(1994\)](#) for sodium channel myotonias characterized by an exacerbation of muscle stiffness by potassium ingestion and/or cold environment. The name has been approved by international experts at a European Neuromuscular Centre Workshop on Paramyotonia, Potassium-aggravated Myotonia and Periodic Paralyses ([Rudel and Lehmann-Horn, 1997](#)). The potassium-aggravated myotonias (PAM) include myotonia fluctuans, myotonia permanens, acetazolamide-responsive myotonia and painful myotonia, i.e., a spectrum of diseases with overlapping clinical features which have in common, in contrast to paramyotonia congenita and hyperPP, no weakness.

In the mildest form, the affected individuals might not be aware of a muscle problem. These patients may present with a severe generalized muscle stiffness after intravenous administration of depolarizing muscle relaxants. Others experience stiffness that tends to fluctuate from day to day, hence the name myotonia fluctuans ([Ricker et al., 1990](#)). Usually, the patients become stiff 10–30 min after strenuous work ([Fig. 3.4](#)). This *delayed* myotonia should not be confused with *paradoxical* myotonia. Usually, the limb muscles show a warm-up phenomenon, and paradoxical myotonia is restricted to the eyelid muscles. The patients do not experience muscle weakness and their muscles are not substantially sensitive to cold. They develop severe stiffness also following oral ingestion of potassium and administration of other depolarizing agents such as anticholinesterases. The sometimes painful stiffness may hinder the patient's movements for several hours. The sodium channel mutations S804F and G1306A ([Fig. 3.5](#)) have been identified to cause *myotonia fluctuans* ([Ricker et al., 1994b](#)). Anesthetic complications of G1306A carriers have also been reported by others ([Vita et al., 1995](#)).

The intermediate form of PAM is similar to Thomsen's disease. However, in contrast to patients with Thomsen's disease is the patients respond very well to acetazolamide (*acetazolamide-responsive myotonia*; [Trudell et al., 1987](#); [Ptacek et al., 1994](#)), develop stiffness not



**Fig. 3.4.** Delayed myotonia in a myotonia fluctuans patient. The upper trace shows the surface EMG and the lower trace the myogram of the finger flexors. The first two forceful isometric contractions (lasting 10 s and a second shorter period) were not associated with myotonia. However, short contractions, performed after a rest of 2 and 10 minutes, elicited severe electrical myotonia and slowed relaxation (delayed myotonia). Adapted from Ricker et al. (1990).



**Fig. 3.5.** Membrane topology model of the voltage-gated sodium channel. A. The skeletal muscle  $\alpha$ -subunit functions as an 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. B. When inserted in the membrane, the four repeats of the protein fold to generate a central pore as indicated schematically. C. The different symbols used for the known mutations leading to potassium-aggravated myotonia, paramyotonia congenita and two types of periodic paralysis.

only after potassium ingestion but also after exposure to cold (V1589M: Heine et al., 1993; Mitrovic et al., 1994; V1293I: Koch et al., 1995; L266V: Wu et al., 2001; F1705I: Wu et al., 2005), and/or suffer from exercise-induced painful muscle cramping (V445M: Rosenfeld et al., 1997; V1589M: Orrell et al., 1998; L266V:

Wu et al., 2001). In contrast to paramyotonia, no cold-induced weakness occurs.

The most severe type of sodium-channel myotonia is characterized by persistent and severe myotonia and is therefore called *myotonia permanens*. Molecular biology has revealed that this condition is caused by a specific

mutation (G1306E, Fig. 3.5) in the *SCN4A* gene product (Lerche et al., 1993; Mitrovic et al., 1995). The continuous electrical myotonia leads to a generalized muscle hypertrophy that also involves muscles of face, neck and shoulders. When the myotonia is aggravated, as by intake of potassium-rich food or by exercise, ventilation can be impaired by stiffness of the thoracic muscles. Children are particularly at risk of suffering acute hypoventilation leading to cyanosis and unconsciousness. This has led to confusion with epileptic seizures and resulted in treatment with anticonvulsants which block sodium channels. The severely affected patients could probably not survive without continuous treatment. One patient was misdiagnosed as having the “myogenic type” of Schwartz-Jampel syndrome (Spaans et al., 1990), until electrophysiological studies revealed impaired sodium-channel inactivation (Lehmann-Horn et al., 1990b) and finally, molecular genetics showed a *SCN4A* mutation (Lehmann-Horn et al., 2004). A further indication of the severity of the myotonia is that all patients reported to date are sporadic. There are no reports of familial cases and affected patients have not had children. Because of the severity of the disease, ingestion of potassium or exposure to cold may cause further worsening and should be avoided.

#### 3.4.1.1. Electromyography

In addition to the short-lasting myotonic bursts found in the chloride-channel myotonias, long-lasting runs of fibrillation-like activity with slow or no changes in action potential frequency and amplitude are found in sodium channel PAM. In myotonia fluctuans, the EMG demonstrates myotonic bursts even when clinical myotonia is absent. As to be expected, muscles of myotonia permanens patients reveal continuous myotonic activity.

#### 3.4.1.2. Microscopy

Despite the seemingly drastic differences in clinical severity, the histological findings do not systematically differ (Jurkat-Rott et al., 2002). In myotonia fluctuans, light microscopy may show a normal appearance or increased central nuclei and fiber diameter variation. Subsarcolemmal vacuoles representing a nonspecific enlargement of the T-tubular system may be found by electron microscopy (Ricker et al., 1990). In myotonia permanens, the subsarcolemmal myoplasmic space and mitochondria may be increased, and focal disarray or interruption of myofibrils and disappearance of Z-disks, involving one or more sarcomeres, may be seen. In these areas, glycogen particles and elongated or branched mitochondria can be found. Between the bundles of myofibrils, membrane-bound vacuoles may be visible which are empty, or filled with fine granular material or electron-dense whorls.

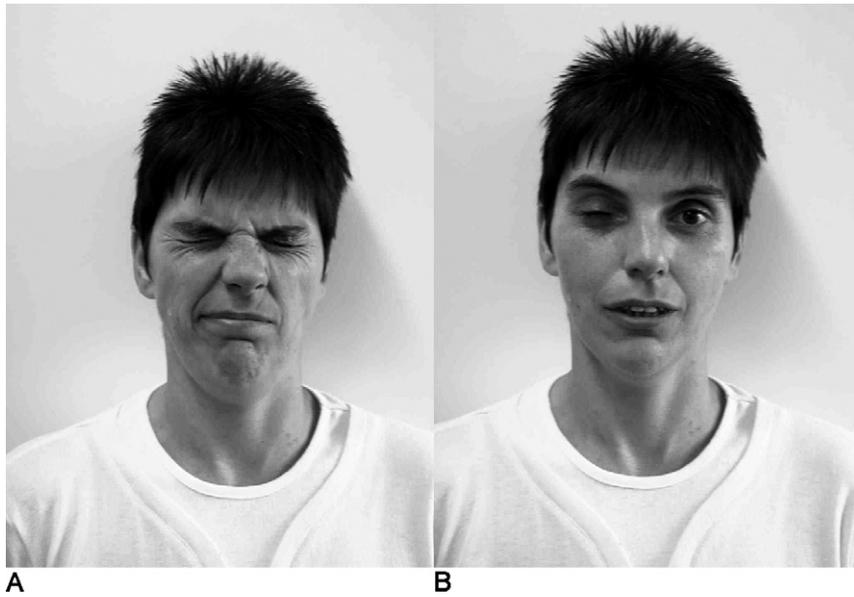
#### 3.4.2. Paramyotonia congenita

Paramyotonia congenita (PC) is inherited as an autosomal dominant (MIM 168300). Signs are present at birth and often remain unchanged throughout life. The cardinal symptom is cold-induced muscle stiffness that increases with continued activity (paradoxical myotonia). On repeated strong contractions of the orbicularis oculi, the opening of the eyelids is increasingly impeded; finally the eyes cannot be opened to more than a slit. As a rule, muscles are bilaterally and symmetrically affected. Many patients exhibit the lid-lag phenomenon and some have percussion myotonia. The motility of the eyeballs may be hampered, which may lead to short bouts of diplopia. Also, swallowing may be impeded for short periods of time. These symptoms, however, tend to be transient. In rare cases, the paramyotonic muscles seem to be somewhat swollen. Muscle atrophy or hypertrophy are not typical for the disease.

In the cold (even in just a cool wind), the face may appear mask-like, and the eyes cannot be opened for several seconds or minutes (Fig. 3.6). Working in the cold makes the fingers so stiff that the patient cannot move them for several minutes. Under warm conditions, most patients have no complaints because impaired muscle relaxation improves at higher temperatures. Other patients have stiff limb muscles in a warm environment; the stiffness improves on continued exercise and displays the paradoxical reaction only on cooling. On the whole, the duration and degree of the paramyotonic reaction of muscles depends on the duration and intensity of cooling, but there are also individual differences in susceptibility.

A few patients claim that emotional factors or hunger aggravate their condition. In many cases alcohol has an obvious beneficial effect. Some patients believe that they are more susceptible to paramyotonia when they have a cold. Paramyotonia may become more severe during pregnancy, so that the leg muscles stiffen even under warm conditions. Hypothyroidism also causes generalization of paramyotonia and aggravates both muscle stiffness and weakness. All movements are then severely hampered, even independently of cooling.

An estimate of the prevalence of paramyotonia congenita seems almost impossible to obtain, because most of the affected individuals never consult a doctor for their symptoms. Moreover, when a paramyotonic patient requires medical help for another reason, they hardly mention their paramyotonic symptoms. Although paramyotonia can be troublesome, it is often a harmless abnormality or a familiar peculiarity that the sufferer simply tolerates. Patients feel that they must make the best of their condition, as did their ancestors, an opinion reinforced when they encounter medical ignorance. On the whole, patients tend to hide their

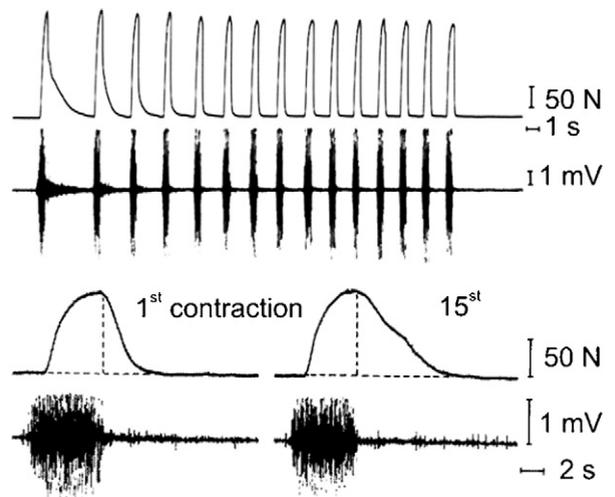


**Fig. 3.6.** Effects of local cooling on a paramyotonia congenita patient. After the patient's right eye was cooled for 10 min, she was asked to close her eyes forcefully (A) and the open them fast (B). The cooled right eyelid remained involuntarily closed for almost a minute.

family anomaly as much as possible, even from close relatives, because they have often experienced embarrassing situations and been ridiculed. On the other hand, paramyotonia patients readily share their experiences with each other. Older patients report that their paramyotonia improved with age. In many of these cases, however, it was not clear whether the paramyotonia had really improved or whether the patients had learned to adapt to it by avoiding exposure to cold and by taking advantage of improving standards of living. Life expectancy is not decreased by paramyotonia.

In most families, the stiffness gives way to flaccid weakness or even to paralysis on intensive exercise and cooling (Fig. 3.7; Haass et al., 1981). Some, but not all, families with PC also have attacks of generalized hyperkalemic periodic paralysis for an hour or less (see below), provoked by rest after strong exercise or by potassium ingestion. In contrast, the cold-induced weakness usually lasts for several hours even when the muscles are promptly rewarmed. During a severe paralytic attack, the muscle stretch reflexes are diminished or absent.

Paramyotonia mutations are situated either in the inactivation gate, the intracellular loop connecting domains III and IV (T1313M: McClatchey et al., 1992; T1313A: Bouhours et al., 2004), in the voltage sensor of repeat IV (R1448H/C/S/P: Ptacek et al., 1992; Chahine et al., 1994; Lerche et al., 1996; Bendahhou et al., 1999) or in the intracellular S4-S5 loops (F1473S: Lerche et al., 1997; A1152D: Bouhours et al., 2005). Paramyotonia families with R1448 substitutions (Fig. 3.5) also have



**Fig. 3.7.** Contractions of a paramyotonia patient at different temperatures. Periods of voluntary isometric muscle contractions (in Newton) and the corresponding surface EMG activity underneath (modified from Haass et al., 1981). The patient was asked to maximally contract his muscles for about 3–5 s and then to relax. The upper two traces show the warm-up phenomenon at 37°C, the lower two traces the paradoxical myotonia, i.e., slowed relaxation during exercise after 30-min cooling of the forearm in water of 15°C. Note the reduced muscle strength after cooling.

attacks of generalized hyperkalemic periodic paralysis, provoked by rest or ingestion of potassium, lasting for an hour or less. In contrast to the short-lasting spontaneous weakness in hyperkalemimic periodic paralysis and

paramyotonia, the cold-induced paramyotonic weakness usually lasts several hours even when the muscles are immediately rewarmed. Also, carriers of other mutations show overlapping features: in a Japanese pedigree, the mutation M1370V resulted in paramyotonia in one family member and in hyperkalemic periodic paralysis in others (Okuda et al., 2001). Also, with hyperkalemic periodic paralysis mutations such as M1360V, T704M and M1592V (Fig. 3.5), paramyotonic signs have been reported in single families (Kelly et al., 1997; Wagner et al., 1997; Kim et al., 2001; Brancati et al., 2003). I693T has been published as a paramyotonia mutation (Plassart et al., 1996) although it causes weakness in the absence of stiffness and would therefore be compatible with a hyperkalemic periodic paralysis mutation.

#### 3.4.2.1. Electromyography

Electrical discharges may be absent at normal or increased temperatures, but cooling elicits fibrillation-like spontaneous activity (Haass et al., 1981). Depending on the temperature and the resulting membrane potential between the action potentials, the electrical activity may vary between myotonic discharges and long-lasting repetitive complex discharges (Weiss and Mayer, 1997). In the transient phase, during which periodic paralysis emerges from the paramyotonic state, silent contractures can accompany the myotonic contractions. Extracellular recordings from excised muscle bundles, with electrodes that detect all electrical activity, reveal that part of the slowed relaxation following direct electrical stimulation and cooling are not caused by action potentials (Ricker et al., 1986). The most likely explanation is that sustained membrane depolarization evokes a long-lasting contracture and also blocks subsequent action potentials generation. This process finally leads to lack of insertional and voluntary EMG activity.

#### 3.4.2.2. Microscopy

In paramyotonia, light microscopy may be unremarkable except for non-specific changes such as occasional central nuclei, variation of fiber diameter and occasional hypertrophic, atrophic, split and regenerating fibers (Jurkat-Rott et al., 2002). ATPase type 2A fibers may be hypertrophied and the number of type 2B fibers may be decreased as in the chloride channelopathies. However, normal muscle fiber area and distribution of fiber types 1, 2A and 2B have also been described. In some areas, there may be focal myofibrillar degeneration with myelin bodies, lipid deposits, occasional subsarcolemmal vacuoles (without periodic acid-Schiff (PAS)-positive material) and tubular aggregates. Muscle fiber degeneration followed by phagocyte invasion and fatty replacement may occur, perhaps induced by

the cold-induced attacks of weakness (see also periodic paralysis) and structural alterations due to electrolyte shifts or periods of muscle inexcitability.

#### 3.4.3. Hyperkalemic periodic paralysis

Hyperkalemic periodic paralysis (hyperPP) is characterized by attacks of transient myotonic stiffness which are followed by flaccid weakness and hyperkalemia. Between attacks, serum potassium and muscle strength are normal, but a chronic progressive proximal myopathy may develop in older patients. The paralytic attacks usually begin in the first decade of life and increase in frequency and severity over time into adulthood. After about the age of 45 years, the frequency of attacks declines considerably. Potassium-rich food or rest after exercise can precipitate an attack. Cold environment and emotional stress also provoke or worsen the attacks. A spontaneous attack commonly starts in the morning before breakfast, lasts for 15 minutes to an hour, and then disappears. Usually, cardiac arrhythmia or respiratory insufficiency do not occur. Between attacks, hyperPP is usually associated with a mild myotonia which may be detectable only by EMG. If myotonia is aggravated by cold and exercise, the diagnosis of paramyotonia congenita is preferred.

HyperPP mutations are situated at several disseminated intracellularly faced positions of the sodium-channel protein potentially involved in the formation of the inactivation apparatus (Lehmann-Horn and Jurkat-Rott, 1999). They lead to incomplete channel inactivation and a pathologically increased sodium current which is associated with a sustained muscle-fiber depolarization. The degree of depolarization determines the clinical symptoms: the non-inactivating mutant channels open the normal channels of a slightly depolarized membrane thereby generating repetitive muscle action potentials (hyperexcitability); at stronger depolarizations, the population of genetically normal sodium channels is inactivated and the muscle paralyzed as no action potentials can be generated. Although myotonia and paralysis are clinically the opposite the pathomechanism is qualitatively the same. The dominance of the mutation results from the fact that the mutation is decisive for the cell excitability. Elevation of extracellular potassium triggers an attack because it depolarizes the membrane.

Detailed information on this disease is given in chapter 4 (Periodic paralysis).

#### 3.4.4. Animals with sodium-channel myotonias

A condition equivalent to human hyperkalemic periodic paralysis in man has been identified in the Quarter horse, a common breed of racehorse in the USA (Cox,

1985). It has the highest incidence of all known inherited disorders of horses. The symptoms are similar to those described above for the human disease, but the condition seems to be more serious than in man as some affected horses have died during attacks. The hyperexcitability of muscles causes hypertrophy, and the resulting aesthetic makes them show winners rather than race winners. A sodium-channel mutation was identified in the equine muscle sodium channel (Rudolph et al., 1992) that causes functional alterations comparable to that observed in human hyperPP at the molecular level (Cannon et al., 1995; Hanna et al., 1996). All affected horses (4.4% of the Quarter horses in the USA) trace to the sire *Impressive* as first-, second- or third-generation descendants. This is an ideal model for the study of the cellular and physiological factors dictating the onset and severity of attacks and the relationship between exercise, serum potassium levels, catecholamines and other factors influencing muscle metabolism. Study of hyperkalemic horses revealed the first correlation of mutant relative to normal mRNA level as a likely determinant of clinical severity in a dominantly inherited disease (Zhou et al., 1994). Accordingly, homozygous animals have laryngeal and pharyngeal dysfunction during exercise while heterozygous animals do not, even though their weakness and myotonia are comparable (Carr et al., 1996).

#### 3.4.5. Diagnosis and molecular pathogenesis

Potassium-aggravated myotonias, paramyotonia and hyperPP have a similar pathogenesis, involving the voltage-gated sodium channel which is essential for the generation of the muscle action potential. Gain of function mutations cause a gating defect of the sodium channel that leads to slowed and/or incomplete channel inactivation (for review see Lehmann-Horn and Jurkat-Rott, 1999) and an uncoupling of inactivation from activation (Chahine et al., 1994). As a result of the increased membrane permeability, more sodium ions than normal are conducted and the fibers depolarize (Lehmann-Horn et al., 1987; Lerche et al., 1993). The pathologically increased inward sodium current through the mutant channels generates repetitive action potentials and myotonia (PAM). Cooling increases the inactivation defect of paramyotonia channels (Fig. 3.8; Mohammadi et al., 2003). Stronger sustained depolarizations, as in paramyotonia, lead to inactivation of the remaining sodium channels, abolition of action potentials and hence muscle weakness. The sodium pump, which is partly blocked by cooling, cannot compensate for this large inward sodium current, which becomes osmotically relevant and draws water into the fibers

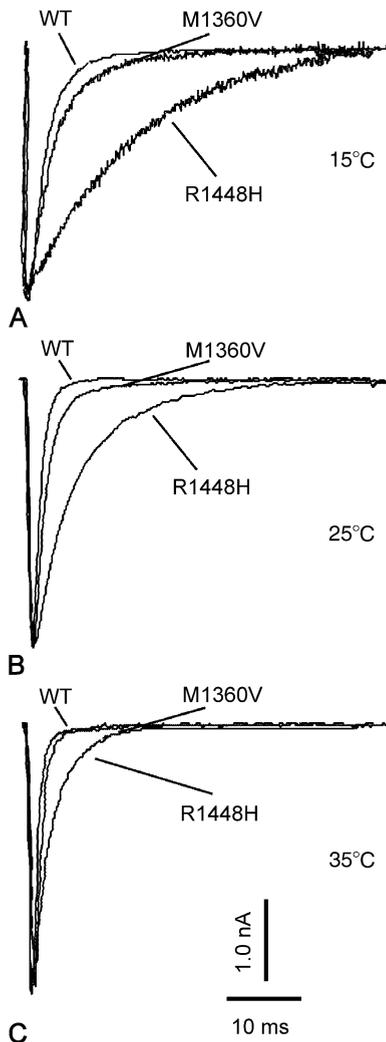
(Weber et al., 2006). The resulting electrolyte imbalance prolongs the weakness, which usually lasts several hours even when the muscle has been immediately rewarmed. In contrast, PAM fibers tend to repolarize to normal membrane potentials and therefore do not become paralyzed (Weber et al., 2006).

Given a clinical or EMG diagnosis of myotonia, the first step is to exclude myotonic dystrophy. Although other clinical features may be suggestive, this can only be achieved with certainty by molecular genetics (exclusion of DM1 and DM2 nucleotide repeat expansions). If exclusion is successful, further clarification is based on provocation tests (potassium ingestion, cooling) and molecular genetics (screening for mutations in *SCN4A* and *CLCN1*). The identification of a specific mutation may aid advising about prognosis. As histology is not specific, and a muscle biopsy should only be considered in those patients whose diagnosis remains unclear after all other diagnostic tools have been used.

#### 3.4.6. Therapy

Most patients with Thomsen and some with Becker myotonia can manage well without medication. They tend to keep their muscles in the warmed-up state by continuous slight movements. However, many patients with Becker myotonia require long-term medication. The myotonic stiffness responds to local anesthetics and class I antiarrhythmic drugs, the lidocaine analogs. Of the many drugs tested that can be administered orally, mexiletine is the drug of choice (up to 200 mg mexiletine three times daily). As the therapeutic index of mexiletine is narrow, patients and doctors must monitor for symptoms and signs indicating drug toxicity. An ECG should be performed before and after starting treatment, and after dose increases. At higher doses, the serum level should be checked whenever the dose is increased. Complications include nausea, paresthesia, tremor, seizures, alterations in cardiac excitability and conduction, hypotension and coma. Mexiletine can be administered to children provided they are kept well-hydrated at all times.

Mexiletine preferentially blocks the non-inactivating mutant sodium channels that reopen abnormally frequently (Mohammadi et al., 2005). Thus, mexiletine has a much greater beneficial effect in sodium-channel myotonias than in chloride-channel myotonia. Patients with myotonia permanens need long-term continuous therapy. The drug is also very effective in preventing and reducing the degree of cold-induced stiffness and weakness in PC. These patients may wish to prevent the cold-induced stiffness and weakness at special events, e.g., winter sports. For this purpose, a temporary use of mexiletine, beginning 2–3 days before the event,



**Fig. 3.8.** Superimposed whole-cell current traces for a depolarization from  $-100$  mV to  $0$  mV for wild-type (WT) and the R1448H and M1360V mutant channels at (A)  $15^{\circ}\text{C}$ , (B)  $25^{\circ}\text{C}$ , (C)  $35^{\circ}\text{C}$ . M1360V causes temperature-insensitive hyperPP; R1448H causes temperature-sensitive paramyotonia congenita. Adapted from Mohammadi et al. (2003).

can be sufficient. The antimyotonic drugs have no effect on the spontaneous attacks of weakness associated with hyperkalemia that also occur in patients with PC (Ricker et al., 1983).

Carbonic anhydrase inhibitors, such as acetazolamide and dichlorophenamide, are an alternative treatment for patients with sodium-channel myotonias. The benefit of these drugs can be judged from the fact that one of the sodium-channel myotonias was dubbed acetazolamide-responsive myotonia (Trüdel et al., 1987). Acetazolamide can improve paramyotonic stiffness (Benstead et al., 1987) but may induce weakness

in PC patients (Griggs et al., 1978) and — like fenoterol — exacerbate chloride-channel myotonia (Ricker et al., 1978a; Bretag et al., 1980).

Independent of the molecular etiology of the myotonia, pregnancy (Risseuw et al., 1997; Lacomis et al., 1999; Newman et al., 1999) and hypothyroidism (Sansone et al., 2000) can unmask subclinical myotonia; vice versa, myotonia that occurs in hypothyroid patients responds to thyroxin. Fasting and stress aggravate myotonic stiffness. A myotonic reaction can be also exacerbated by depolarizing agents such as potassium, suxamethonium and anticholinesterases (Mastaglia, 1982; Lehmann-Horn and Iaizzo, 1990a). Administration of depolarizing muscle relaxants usually causes isolated masseter spasm. Respiratory and occasionally other skeletal muscles may also become stiff. Subsequent impaired intubation and mechanical ventilation may result in a life-threatening situation. As myotonia is aggravated by hypothermia-induced muscle shivering, the patients should be kept warm in the operation theatre.

Of the various types of sodium channel myotonia, the incidence of anesthetic events seems to be highest in families with myotonia fluctuans (Ricker et al., 1990; Heine et al., 1993; Ricker et al., 1994b; Vita et al., 1995). Most likely, it relates to the frequent absence of clinical signs prior to the operation. Thus, the anesthesiologist is not aware of the condition. In the other diseases, patients report that they have myotonia or attacks of weakness, and depolarizing agents can be avoided thereby lowering the risk of an adverse event. PC patients may be paralyzed for several hours upon awakening from general anesthesia. Preventive therapy before surgery, and maintaining a normal body temperature will help to prevent such attacks (Ashwood et al., 1992).

As myotonic patients may develop local or generalized muscle spasms, and such spasms can cause an increase in body temperature and elevated CK values, they are often considered to be susceptible to malignant hyperthermia. However, the specific clinical details and the results of in vitro contracture testing have not been detailed in case reports suggesting an association with malignant hyperthermia (Paasuke and Brownell, 1986; Thomas et al., 1988; Heiman-Patterson et al., 1988). Most likely, these anesthesia-related episodes are caused simply by severe myotonic reactions (Lehmann-Horn and Iaizzo, 1990a; Allen, 1993; Iaizzo and Lehmann-Horn, 1995). In contrast to the silent muscle contractures in malignant hyperthermia (Jurkat-Rott et al., 2000) which well respond to dantrolene, myotonic contractions result from bursts of action potentials and theoretically are more likely to be relieved by lidocaine than by dantrolene. The latter may reduce the contraction force but not the primary hyperexcitability of the membrane.

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