Skeletal muscle channelopathies: myotonias, periodic paralyses and malignant hyperthermia

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23.1. Introduction

23.1.1. Membrane excitability and coupling of excitation to contraction

Motoneuron activity is transferred to skeletal muscle at the neuromuscular junction generating a sarcolemmal action potential that propagates from the endplate to the tendon and along the transverse tubular system (TTS). This membrane region projects deeply into the cell to ensure even distribution of the impulse. The upstroke of the action potential is mediated by opening of the voltage gated sodium channels (encoded by the SCN4A gene located on chromosome 17q13.1-3 and its accessory beta-subunit encoded by SCN1B on chromosome 19q13.1) that elicit a sodium inward current with rapid activation kinetics. Repolarization of the membrane by fast sodium channel inactivation is supported by opening of delayed rectifier potassium channels that mediate an outward potassium current. Buffering of after-potentials is achieved by a high chloride conductance near the resting potential resulting from the homodimeric chloride channel, CIC-1, encoded by the gene CLCN1 on chromosome.

At specialized junctions in the TTS, the signal is transmitted from the tubular membrane to the sarcoplasmic reticulum (SR) causing the release of calcium ions into the myoplasm which activate the contractile apparatus. This process is called excitation-contraction coupling. Mainly two calcium channel complexes are involved in this process, the voltage-gated pentameric dihydropyridine receptor located in the TTS (encoded by the CACNA1S gene on chromosome 1q31-32 and genes for accessory subunits) and the homotetrameric ryanodine receptor of the SR (encoded by the RYR1 gene on chromosome 19q13.1).

23.1.2. Channelopathies: episodic stiffness and weakness

Membrane excitability is regulated by voltage-gated ion channels which are essential for the stabilization of the resting membrane potential and the generation of the action potential. It is therefore not surprising, that ion channels are involved in the pathogenesis of diseases of skeletal muscle. Channelopathies are defined as episodically recurring disorders caused by a pathology of ion channel function (Hoffman et al., 1995). Clinically, skeletal muscle ion channelopathies appear as episodes of muscle stiffness or weakness triggered by typical circumstances such as cold, exercise, oral potassium load, or drugs. According to the mode of transmission and potassium sensitivity, four forms of myotonia and paramyotonia are distinguished: dominant (potassium-insensitive) myotonia congenita, recessive myotonia congenita, dominant potassium-aggravated myotonia, and dominant paramyotonia congenita. Myotonic dystrophies type I and 2 are chronic progressive multisystemic diseases of dominant inheritance and not true channelopathies. They are discussed in this chapter because of the common feature of myotonia which is thought to be caused by a pathology of ion channel expression.

While myotonia is brought about by uncontrolled repetitive firing of action potentials leading to involuntary muscle contraction, lack of action poten-
tials or muscle inexcitability results in weakness. Three dominant types of episodic weakness with or without myotonia are either distinguished by the serum potassium level during the attacks of weakness, hyper- and hypokalemic periodic paralysis or by concomitant clinical features such as cardiac arrhythmia and facial dysmorphia, Andersen's syndrome.

An electrically silent muscle stiffness triggered by volatile anesthetic agents and depolarizing muscle relaxants as found in malignant hyperthermia is not associated with myotonic runs. It is based on uncontrolled intracellular calcium release via the ryanodine receptor that is not preceded by action potentials. An acute, potentially lethal crisis is characterized by muscle hypermetabolism, rhabdomyolysis, body temperature elevation, muscle rigidity, and cardiac arrhythmia.

23.2. Classical myotonia congenita: chloride channel myotonias

23.2.1. Dominant Thomsen and recessive Becker myotonia

Myotonia congenita appears in two forms: Thomsen's disease (MIM 160800), or dominant myotonia congenita (DMC), the first myotonic disease described (Thomsen, 1876), and Becker myotonia (MIM 255700), or recessive generalized myotonia (Becker, 1977), here termed recessive myotonia congenita (RMC). Both disorders are slowly or non-progressive, usually non-dystrophic, and caused by allelic mutations of the gene coding for the chloride channel of the skeletal muscle fiber membrane (Koch et al., 1992). They are referred to as chloride channel myotonias.

In DMC, the myotonia is usually recognized in early childhood, but the milder cases may go unrecognized until late childhood. The myotonia is generalized; the legs are often most affected, causing the children to fall frequently. The cranial as well as arm and hand muscles can be severely affected, and it may be difficult for the patients to grasp objects. Chewing is sometimes impaired. The myotonic stiffness is most pronounced when a forceful movement is abruptly initiated after the patient has rested for 5 to 10 min. For instance, after making a strong fist, the patient may not be able to extend the fingers fully for several seconds. The myotonia decreases or vanishes completely when the same movement is repeated several times (warm-up phenomenon), but it recurs after a few minutes of rest. The patient may experience much difficulty while getting up from a chair or stepping into a bus in a hurry. On rare occasions, a sudden, frightening noise may cause instantaneous generalized stiffness; the patient may then fall to the ground and remain rigid and helpless for some seconds or even minutes. Myotonic signs persist throughout life. The myotonia may increase with pregnancy, but this usually doesn't create a major problem. Hypothyroidism may worsen the myotonia. Contrary to the opinion of many patients, cold does not substantially worsen the myotonic stiffness and slowed relaxation (Ricker et al., 1977).

Upon examination, DMC patients may have hypertrophied muscles and an athletic appearance. Their muscle strength is normal or even greater than normal and they can be quite successful in those sports where strength is more important than speed. Tapping of the muscle produces an indentation that persists for several seconds (percussion myotonia). Lid lag is usually present, and in some patients, myotonia of the lid muscles causes blepharospasm after forceful eye closure. The muscle stretch reflexes are normal and muscle pain is usually not present.

Members of a given DMC family can be affected to different degrees. In a few kinships, the myotonia is consistently very mild and almost undetectable; this was considered a special form and termed myotonia levior. As the inheritance and the molecular pathogenesis is the same as in Thomsen's disease, the term should be abandoned (Lehmann-Horn et al., 1995).

The clinical picture of RMC resembles that of DMC. A few special points are worth mentioning. In many patients, the myotonia is not manifest until the age of 10 to 14 years or even later, but in a few it is obvious already at the age of 2 to 3 years. The severity of the myotonia may slowly increase for a number of years, but usually not after the age of 25 to 30. In general, the myotonia is more severe than in DMC. Thus, RMC patients are more handicapped in daily life, especially by severe myotonic stiffness affecting the leg muscles. They frequently fall down and have gait problems. Muscle shortening due to continuous contractions may limit bilateral dorsiflexion of the wrist or foot. Severely affected patients walk on tiptoes and develop a compensatory lordo-
sis. The leg and gluteal muscles are often markedly hypertrophied, whereas the neck, shoulder and arm muscles appear poorly developed – especially in old age – resulting in a characteristic disproportionate figure. Also very disabling is a peculiar transient weakness affecting especially the hand and arm muscles (see below). Patients with severe RMC are limited in their choice of occupation and they are unsuited for military service. Life expectancy is normal. Alcohol can improve the condition, hunger, emotion or fatigue usually do not aggravate the myotonia.

23.2.2. Clinical neurophysiology of the chloride channel myotonias

23.2.2.1. Electromyographic (EMG) findings in chloride channel myotonias

The electrophysiological correlate of myotonia is – independent of the channel type affected – hyperexcitability of the sarcolemma which causes uncontrolled repetitive firing of action potentials following an initial voluntary activation. This myotonic reaction prevents the muscle from immediate relaxation which the patients experience as muscle stiffness.

Standard EMG – Spontaneous activity. In Thomsen and Becker patients, the myotonic activity can be observed in all routinely examined skeletal muscles. In the EMG, repetitive firing is typically observed as myotonic bursts which are elicited easily by needle insertions or slight mechanical manipulations like tapping. The slowed relaxation which patients experience as muscle stiffness is strongly correlated to electrical activity as could be shown in biopsied muscle specimens in vitro (Iaizzo and Lehmann-Horn, 1990). Interestingly, this is in contrast to the cold-induced stiffness in paramyotonia congenita. Typical are short bursts of action potentials appearing as triphasic spikes or as positive sharp waves with amplitude and frequency modulation lasting <1 s and sometimes up to 10 s (Ricker and Meinck, 1972a). The most often mentioned but rare pattern, best recognizable in the acoustic EMG, is that of a myotonic “dive-bomber”. This is a short discharge characterized by first an increase in frequency and decrease in amplitude and then a decrease in frequency and increase in amplitude. Much more frequent though, are short bursts characterized by a rising frequency and a falling spike amplitude. Apart from these typical and diagnostically relevant myotonic runs, other forms of spontaneous activity do occur, such as positive sharp waves at lower frequency or more complex discharges like rhythmic doublets and triplets.

In RMC families, the heterozygous parents of affected offspring can sometimes be identified by having short (rarely longer than 1 s) myotonic discharges of low amplitude on EMG without clinical manifestation. In addition to myotonic runs, heterozygous carriers showed very brief complex repetitive discharges, increased insertional activity, and prolonged trains of rhythmic, low-frequency (<60 Hz) positive waves lasting several seconds. In two thirds of RMC families, at least one of the parents exhibited this spontaneous activity (Deymeer et al., 1999).

Standard EMG – other parameters. Motor unit potentials in both forms of myotonia congenita are usually normal. In RMC, however, myopathic changes like multiphasic or low amplitude potentials can be observed (Streib, 1987). Rarely, specific CIC-1 mutations may even induce dystrophic variants of the disease with myopathic motor unit potentials seen in all extremities (Nagamitsu et al., 2000). CMAP amplitudes and nerve conduction velocities are normal, unless in the period of transient weakness (see below).

23.2.2.2. Warm-up phenomenon

The stiffness is initiated by a forceful muscle contraction, particularly after a period of rest of at least 10 min. This may not necessarily pertain to the first contraction which may be relatively unimpeded, but becomes increasingly obvious following the second and third short but forceful contractions. The disturbance of muscle relaxation after further contractions gradually disappears, a phenomenon which is called warm-up phenomenon, the pathophysiological mechanism of which is still unknown.

23.2.2.3. EMG studies during transient weakness

In the more severe Becker type, the stiffness is usually associated with the symptom of transient weakness that depends on the patient’s past activity in a similar way as the stiffness. This is best demonstrated when the patient makes a tight fist after a period of rest: the force exerted by the finger flexors vanishes almost completely within a few seconds. When the patient lifts a heavy object, it may
slide out of the hand because of loss of muscle strength (Ricker et al., 1978; Deymeer et al., 1998). In a similar situation, a patient with dominant MC would be unable to release the handle for a while. With repeated muscle contractions, the force returns within 20 to 60 s (Fig. 1).

Electrophysiologically, the weakness occurring experimentally upon repetitive stimulation is accompanied by a decrease of the CMAP amplitude, as was shown in a large number of studies (e.g. Ricker and Meinck, 1972b; Brown, 1974; Aminov et al., 1977; Ricker et al., 1978; Deymeer et al., 1998). In a more detailed investigation using surface EMG, Zwarts and Van Weerden (1989) also showed, that the muscle fiber conduction velocity (MFCV), the median frequency of the power spectrum and the integrated EMG decline during transient paresis in Becker myotonia. Multi-channel surface EMG, yielding a high spatial-temporal resolution, revealed a gradually developing decrease in peak-to-peak amplitude of the motor unit action potentials from endplate towards tendon in parallel with the force decline. This deteriorating membrane function temporally leads to a complete intramuscular conduction block within s in RMC (Drost et al., 2001). Using single fiber EMG, qualitatively similar results could be obtained. Upon repetitive stimulation, the muscle fiber action potential showed a progressive decrease in amplitude, marked deformation, and a varying latency occurring only after a few stimulations (Lagueny et al., 1994; Trontelj and Stålberg, 1995).

All of these changes were observed in both DMC (Thomsen) and RMC (Becker), although in the latter disease, the transient weakness occurs much more frequently than in the former one. Consistent with this clinical observation, however, in some of the studies in which patients with both diseases were compared, a more heavy stimulus like a higher stimulating frequency was necessary to induce the same effect in DMC compared to RMC (Lagueny et al., 1994; Deymeer et al., 1998).

**23.2.3. Molecular diagnosis and pathogenesis of the chloride channel myotonias**

The causative gene for dominant Thomsen and recessive Becker myotonia is \textit{CLCN1} 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 independent ion-conducting pores each with a fast opening mechanism of its own, but also with a gate structure common to both pores (for review Fahlke et al., 2001). Over 50 CIC-1 mutations have been identified (Fig. 2) which, according to our data, account for approximately 30% of the cases, making genetic studies quite arduous. While non-sense and splicing mutations always lead to the recessive phenotype, missense mutations are found in Thomsen and Becker myotonia. A few intermediate mutations are even able to generate both modes of transmission probably depending on supplemental genetic or environmental factors. If genetic screening does not yield a result, linkage analysis including additional family members of defined clinical status

**Myotonic runs and transient weakness**

![Myotonic runs and transient weakness in a patient with recessive myotonia congenita (RMC). Left panels: 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. Right panels: 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., 1978.](image-url)
is a very useful tool to confirm clinical diagnosis. An important issue genetically and prognostically (and in some cases diagnostically) is to exclude the repeat expansions causing myotonic dystrophy types 1 and 2.

Functionally, the fast opening mechanism of each pore of the double barrel dimer channel complex is affected by the recessive mutations, whereas a common slow additional gate structure shared with the co-associated subunit is affected by the dominant mutations (Saviane et al., 1999). 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 resulting chloride 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 chloride conductance is drastically reduced in the crucial vicinity of the resting membrane potential (Fig. 3). 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 chloride conductance so much that myotonia develops (at least down to 30%; Palade & Barchi, 1977). Functional alteration of the chloride channels leads to a reduced membrane conductance for chloride decreasing the stability of the membrane potential. Regarding the clinical picture of affected patients, the instability is obviously highest during voluntary muscle activation following rest. Repetitive activity then ensues, giving rise to myotonia. Upon warming-up, the muscle fiber membrane then seems to adapt to the lower chloride conductance. The excessive activity may also lead to slowly progressive depolarization between action potentials causing the transient (or sometimes permanent) weakness. It usually lasts
23.2.4. Differentiation from dystrophic myotonias

Some RMC patients show progressive generalized muscle weakness, severe distal muscle atrophy, and unusually high serum creatine kinase levels (Nagamitsu et al., 2000), making the differentiation from myotonic dystrophies difficult.

Myotonic dystrophy type 1 (DM1)

Myotonic dystrophy (DM1; MIM 160900) is an autosomal dominant multi-organ 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 wasting that begins in the distal limb and cranial muscles. Cataract, retrobulbar hypotension, gonadal atrophy, conduction abnormalities in the heart, hearing deficiencies, and neurocognitive deficits appear quite often in the course of the disease. The mutation of DM1 is an expansion of an unstable CTG trinucleotide repeat in the 3′ untranslated region of the myotonic dystrophy protein kinase (DMPK) gene on chromosome 19q13.3 (for review see Conne et al., 2000). Its pathogenesis, though not yet clearly understood, is different from that of the non-dystrophic myotonias even though ion channels may be involved, e.g. by alternative splicing.

In the congenital form of DM1, general muscle weakness (particularly pronounced in the face) is the leading finding, combined with retarded locomotor and mental development. Myotonia is absent, at least in infancy. A decisive criterion for the diagnosis is the occurrence of myotonic dystrophy in the patient’s mother. Electromyographic investigation is indicated when a suspicion of myotonic dystrophy cannot be ascertained on the basis of clinical and genetic findings. Myotonic activity in the EMG of the mother will then corroborate the suspicion.

**Electrophysiologic findings in myotonic dystrophy type 1 (DM1)**

In the adult form of myotonic dystrophy, myotonic EMG activity is less common than in the non-dystrophic myotonias and unevenly distributed over the muscles of the body. The distal muscles of the
upper extremities, the facial muscles and tibialis anterior show the highest incidence of involvement. Electrical myotonia may be only observed in a few muscles or even absent in obligate gene carriers. In children up to ten years, electrical myotonia is rarely seen, but its incidence increases with age later on. In contrast to the chloride channel myotonias, long-lasting discharges of 2–30 s duration with falling or unchanging frequency and amplitude occur more often than the typical short myotonic runs. The maximal frequency is typically 40–60 Hz and thus lower than in chloride channel myotonia (60–100 Hz). Positive sharp waves and complex repetitive discharges are also very common in DM1. Finally, myopathic changes consisting of short, polyphasic potentials with early recruitment are commonly found, best in forearm extensor and tibialis anterior muscles (Ricker and Meinck, 1972a; Streib, 1987; Pfeilsticker et al., 2001).

Motor and sensory nerve conduction studies frequently show mild signs of peripheral neuropathy. CMAP amplitudes are reduced depending on the degree of dystrophic changes. The exercise test shows a mild to moderate decrement in CMAP amplitude with a quick recovery, which is not seen in DM2/PROMM (see below) (Streib, 1987; Sander et al., 1997, 2000; Kuntzer et al., 2000). Muscle fiber conduction velocity (MFCV) and power spectra as determined by surface EMG are normal in contrast to RMC (Zwarts and Van Weerden, 1989).

Electrophysiologic findings in DM2/PROMM
Electromyographic investigation reveals a broad spectrum of spontaneous activity including myotonic discharges, also in most of those patients without obvious clinical myotonia. The myotonic discharges are often scarce, difficult to detect (multiple muscles have to be investigated) and may be fluctuating (Ricker et al., 1995; Day et al., 1999). They can be provoked by heat and diminished by cold (Sander et al., 1996) but this is not observed in all families (Day et al., 1999; Moxley et al., 2002). In addition to myotonic discharges, fibrillation potentials, positive sharp waves, runs of complex repetitive discharges, brief runs of high-frequency (180–240 Hz), 'neuromyotonia-like' discharges and fasciculation potentials do occur (Ricker et al., 1995; Ricker, 1999). In the original DM2 family, the myotonic discharges were typically brief (0.5–2 s), rarely longer (up to 20–30 s) (Day et al., 1999). A myopathic EMG pattern may be detectable, in particular in the most affected muscles. Nerve conduction studies are usually normal but may be abnormal in single cases (Ricker et al., 1995; Day et al., 1999). Sander et al. (1997, 2000) found a normal exercise test in PROMM/DM2, which was in contrast to DM1 (see above) and might be useful in differential diagnosis.
23.3. Myotonias with and without paralyses: sodium channel myotonias

23.3.1. Potassium-aggravated myotonias (delayed myotonias)

For many families with dominant myotonia thought to have a subtype of Thomsen's disease, a muscle chloride channel disease, molecular genetics revealed mutations in SCN4A, the gene encoding the α-subunit of the adult skeletal muscle voltage-gated Na⁺ channel. In contrast to Thomsen's disease, these patients develop severe stiffness which occurs after a delay following strong exercise or oral ingestion of potassium (potassium-aggravated myotonias, PAM). The spectrum of the degree of myotonia is large, ranging from the mild myotonia fluctuans to the very severe myotonia permanens.

In the mildest form, the affected individuals are not aware of a muscle stiffness or experience stiffness that tends to fluctuate from day to day, hence the name myotonia fluctuans (Ricker et al., 1990, 1994). Most patients do not experience muscle weakness and their muscle stiffness is not substantially sensitive to cold. Although the muscle stiffness is provoked by exercise this type of myotonia should not be confused with paradoxical myotonia. Within a period of exercise, the relaxation time of the contractions is normal or – if increased – shows rather a warm-up than paradoxical myotonia. Paradoxical myotonia, if present, is restricted to the eyelid muscles. However, after rest of several minutes, a single contraction might then produce such a severe stiffness (delayed myotonia) that the patient is unable to move for several hours. This sometimes painful exercise-induced muscle cramping may be induced by or associated with hyperkalemia or other depolarizing agents (Heine et al., 1993; Orrell et al., 1998). Another atypical but related disorder is acetazolamide-responsive myotonia, also known as atypical myotonia congenita (Piatek et al., 1994). In this form, muscle pain may be induced by exercise and the symptoms are alleviated by acetazolamide.

A further disease is characterized by severe and persisting myotonia and is therefore called myotonia permanens (Lerche et al., 1993). Continuous myotonic activity is noticeable on EMG and molecular biology has revealed that this condition is caused by a specific mutation (G1306E) in the SCN4A gene product. The continuous electrical myotonia leads to a generalized muscle hypertrophy including face muscles. Particularly the muscles of the neck and the shoulders are markedly hypertrophied. When the myotonia is aggravated, e.g. by intake of potassium-rich food or by exercise, ventilation might be impaired due to stiffness of the thoracic muscles. Children are particularly at risk from suffering acute hypoventilation leading to cyanosis and unconsciousness. This led to confusion with epileptic seizures and resulted in treatment with anticonvulsants such as carbamazepine which proved beneficial because of their antymytotic properties. Such patients would probably not survive without continuous treatment. One of the patients was misdiagnosed as having the "myogenic type" of Schwartz-Jampel syndrome (Spaans et al., 1990), until electrophysiological studies indicated that sodium channel inactivation was impaired (Lehmann-Horn et al., 1990) and molecular genetics enabled the identification of SCN4A mutations (Lerche et al., 1993). A further indication of the severity of this disease is that all patients reported to date are sporadic cases harbouring a de novo mutation and have no children.

In both myotonia fluctuans and myotonia permanens, depolarising agents such as potassium or suxamethonium may aggravate the myotonia but do not induce weakness. It is well recognized that there is an increased incidence of adverse anesthesia-related events with the use of depolarising relaxants in myotonic disorders. The incidence of such events seems to be highest in myotonia fluctuans families (Ricker et al., 1994; Vita et al., 1995). There seems to be no biological reason for this and it most likely relates to the frequent absence of clinical myotonia in these patients making the anesthesiologists unaware of the condition.

Electrophysiologic findings in PAM

In routine EMG examination, typical myotonic runs are observed in all muscles examined, even during the spells of absence of clinical myotonia. In addition to these short-lasting myotonic bursts which are typical for the chloride channel myotonias, long-lasting runs of fibrillation-like activity with slow or no changes of frequency and amplitude may occur (Fig. 6). These may appear constantly in some patients. When delayed onset myotonia is recorded, the relaxation disturbance can be fully explained by electrical activity which is in contrast to para-
myotonia congenita (see below). There is no alteration of the activity in cold environment, but myotonic runs and fibrillation-like activity are enhanced by potassium intake in parallel with the clinical myotonia. Motor unit potentials appeared normal (Ricker et al., 1990, 1994).

23.3.2. Paramyotonia congenita: paradoxical myotonia and cold-induced weakness

Paramyotonic symptoms are present at birth and remain often unchanged for the entire lifetime. The cardinal symptom of paramyotonia congenita (PC, MIM 168300) is cold-induced muscle stiffness that increases with continued activity (“paradoxical myotonia”, Fig. 4). Particularly in the course of repeated strong contractions of the orbicularis oculi muscles, the opening of the eyelids is more and more impeded until the eyes cannot be opened to more than a slit. In the cold (or even in a cool wind), the face may appear mask-like, and the eyes cannot be opened for several seconds. Working in the cold makes the fingers so stiff that the patient becomes unable to move them within minutes. Many patients exhibit the lid lag phenomenon and some of them percussion myotonia. Muscle pain, atrophy or hypertrophy are not typical for the disease. Under warm conditions many patients have no complaints but some experience myotonia in a warm environment which then mostly presents rather with a warm-up phenomenon.

In most families the stiffness gives way to flaccid weakness or even to paralysis on intensive exercise and cooling. Some, but not all, families with PC also have attacks of generalized hyperkalemic periodic paralysis provoked by rest or ingestion of potassium lasting for an hour or less. In contrast, the cold-induced weakness usually lasts several hours even when the muscles are immediately rewarmed. Muscle relaxation, slightly slowed in some patients at normal temperature, becomes normal when the muscles are warmed.

Electrophysiologic findings in PC

Electrical discharges in the EMG may be absent at normal or increased temperature, but occasional myotonic runs do occur. Upon cooling, a fibrillation-like spontaneous EMG activity develops consistently which is maximal at a muscle temperature of about 29°C. With a further drop in temperature, this spontaneous activity decreases and almost disappears at 24°C when the muscle gets paralysed (Haas et al., 1981). In another single patient, long-lasting repetitive (complex) discharges were reported at room temperature, when the patient had no muscle stiffness, and upon cooling myotonic discharges developed whereas the other activity ceased (Weiss et al., 1997). In patients with myotonia in a warm environment, there was rather a warm-up phenomenon, and clinical myotonia could be related to electrical activity at room temperature. However, the muscle stiffness which developed in all patients upon cooling of the forearm in a water bath of 15°C, was not related to electrical myotonia and interpreted as depolarization-induced contracture of the muscle fibers. With further cooling, most patients develop a flaccid weakness accompanied by electrical silence. Consequently, CMAP amplitudes decrease upon cooling corresponding to the developing weakness. Motor unit potentials as well as motor and sensory nerve conduction studies are normal (Haass et al., 1981; Lehmann-Horn et al., 1984; Ricker et al., 1986; Streib, 1987).

23.3.3. Hyperkalemic periodic paralysis: rest- and potassium-induced paralysis

The disease was first described by Tyler et al., in 1951, and Helweg-Larsen et al., in 1955, and was
extensively investigated by Gamstorp in 1956 who named it “adynamia episodica hereditaria.” The disease differs from hypokalemic periodic paralysis in that it is usually associated with myotonia, at least in the EMG, and that potassium can provoke an attack of weakness and that also a spontaneous attack is associated with an increase in serum potassium. Intake of potassium and glucose have opposite effects in the two disorders, while potassium triggers a hyperkalemic attack and glucose is a remedy, glucose provokes hypokalemic attacks which are ameliorated by potassium intake. The term hyperkalemic periodic paralysis (HyperPP), which stresses the potassium-related distinctions, is preferred (MIM 170500). In general, HyperPP has an earlier onset and more frequent attacks, but these are much shorter and milder than in the hypokalemic form (Gamstorp, 1956).

The attacks usually begin in the first decade of life. Initially, they are infrequent but then increase in frequency and severity. Potassium-rich food or a potassium load as during a provocative test, usually precipitates an attack. Cold environment, emotional stress, glucocorticoids, and pregnancy provoke or worsen the attacks. After strenuous exercise, weakness can follow within a few minutes of rest. A spontaneous attack commonly starts in the morning before breakfast and lasts 15 minutes to an hour, and then disappears. During the day, rest often provokes an attack. Sustained mild exercise after a period of strenuous exercise may postpone or prevent the weakness in the exercising muscle groups and improve the recovery of muscle force (working off) while the resting muscles become weak (Fig. 5).

In the interictal state, the clinical myotonia is usually very mild and never impedes voluntary movements. It is most readily observed in the facial, lingual, thenar, and finger extensor muscles. The generalized weakness is usually accompanied by a significant increase of serum potassium (up to 5 to 6 mM). Sometimes the serum potassium level remains within the upper normal range and only seldom reaches cardiotoxic levels, although it may become life-threatening in very rare cases. As the serum potassium increases, the precordial T waves in the ECG increase in amplitude. When the serum potassium level begins to rise, the serum sodium level falls 3 to 9 mM. This fall is caused by sodium entry into muscle; this, in turn, causes a shift of water into the muscles (observed by some patients as swelling) that causes hemoconcentration and increases the serum potassium level.
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Electrophysiologic findings in HyperPP

Even though myotonic stiffness is often not clinically present, the EMG reveals myotonic activity in most families. In addition to short-lasting myotonic bursts, long-lasting runs of fibrillation-like action potentials with slow changes of frequency and amplitude occur (Fig. 6) which can be provoked by exercise. The myotonia strongly supports the diagnosis of HyperPP and usually excludes HypoPP. At the beginning of an attack, the bursts of fibrillation potentials may increase and explain the sensation of muscle tension. In some patients paresthesia heralds the attack, probably induced by the hyperkalemia.

During a severe attack, insertional EMG activity disappears, voluntary effort elicits few if any motor unit potentials, and the evoked CMAP amplitude is diminished. Intercritally, motor unit potentials, motor and sensory nerve conduction studies are usually normal. Only in patients with a specific, frequent mutation (T704M), a chronic progressive myopathy with a myopathic pattern in the EMG may develop. In about 50% of the T704M carriers, neither clinical nor electrical myotonia is detectable (Subramony and Wee, 1986; Streib, 1987; Ptacek et al., 1991; Lehmann-Horn et al., 1993).

In contrast to PC, cooling does not decrease CMAP amplitudes in HyperPP (Subramony et al., 1986) but may induce muscle weakness in vitro, with a different pathophysiological mechanism than in PC, i.e. without a membrane depolarization (Lehmann-Horn et al., 1987a; Ricker et al., 1989). The exercise test is abnormal in HyperPP as in HypoPP and Andersen's syndrome (see section on HypoPP for a description of the test), as CMAP amplitudes and areas first increase during the short period of exercise and then gradually decrease over a period of 20–40 min. within the post-exercise period. Such a pattern is also seen in secondary periodic paralysis. Thus, the test is helpful to establish the diagnosis of periodic paralysis, but does not distinguish between any of the different forms (McManis et al., 1986; Subramony and Wee, 1986; Kuntzer et al., 2000). However, also rest without exercise may produce weakness in HyperPP (Ricker K, Camacho L, Grafe P, Lehmann-Horn F, Rüdel R: Adynamia episodica hereditaria: what causes the weakness? Muscle Nerve, 10: 883–891, 1989). If this is the case also in HypoPP has not been reported up to now. In PC, the test yields a decrease immediately after exercise with a subsequent return
to baseline (McManis et al., 1986; Subramony and Wee, 1986; Kuntzer et al., 2000).

23.3.4. Specific provocative testing of sodium channel disorders

According to the description above, a provocative test for PAM is an exercise test that measures the muscle stiffness after a forceful and long-lasting voluntary contraction and following short contractions generated by the patient in intervals of several minutes (Ricker et al., 1990). For the differential diagnosis to DMC, the increase in muscle stiffness induced by oral ingestion of potassium can be observed clinically and by relaxation measurements. Potassium must not be administered to patients with myotonia permanens because of the potential stiffness of ventilatory muscles.

The diagnosis of PC can be verified by the following cooling tests: First, the amplitude of the evoked compound muscle action potential is reduced by cooling (Guttmann et al., 1986; Jackson et al., 1994). This test can be easily performed and is supposed to differentiate between PC and HyperPP (Subramony et al., 1986). For the exercise test in PC see section above on electrophysiology of HyperPP. The second test is highly specific but demands facilities which may not be available everywhere: cooled paramyotonia muscles are slow to relax and generate decreased force on maximal voluntary contraction (Ricker et al., 1986). The test is performed by determining the isometric force and relaxation time of the long finger flexor muscles before and after immersing hand and forearm in a water bath of 15°C for 30 min. In some patients, the test reduces the force of contraction by more than 50% and prolongs the relaxation time from 0.5 s up to 50 s. In other patients, the abnormalities appear after an additional maximal voluntary contraction lasting 1 to 2 min. The test is positive if the relaxation is markedly slowed whereby the isometric force exerted by the finger flexors often falls to 10% or less of the pre-test value.

A provocative test for HyperPP to be best performed in the morning prior to carbohydrate ingestion can confirm the clinical diagnosis. This consists of the administration of 2 to 10 g potassium chloride in an unsweetened solution in the fasting state. Serum potassium levels should be determined approximately in intervals of 20 minutes prior to and after ingestion, the ECG monitored and an anesthetist available in case of a wide-spread paralysis involving respiratory muscles. After the ingestion, the patient should avoid all muscle activity. The test is contraindicated in subjects who are already hyperkalemic and in those who do not have adequate renal or adrenal reserve. An abnormally high serum potassium level between attacks suggests secondary rather than primary hyperkalemic periodic paralysis. The provocative test usually induces an attack within the next hour which lasts about 30 to 60 minutes, similarly to spontaneously occurring attacks of weakness. An alternative test without potassium ingestion consists of exercise on a bicycle ergometer for 30 minutes so that the pulse rate increases to 120–160 beats/min followed by absolute rest in bed (Ricker et al., 1989). Serum potassium rises during exercise and then declines to almost the pre-exercise level, as in healthy individuals. At 10–20 minutes after the onset of rest, a second hyperkalemic period occurs in patients but not in normal subjects; during this period, the patients become paralysed. Recordings of the evoked compound muscle action potential during rest and exercise are also helpful in confirming the diagnosis of periodic paralysis (exercise test, see above).

23.3.5. Molecular genetics and pathogenesis of sodium channel myotonia and paralysis

In PAM, there are 8 mutations known in 5 of the 24 exons of the α-subunit of the voltage-gated sodium channel clarifying approximately 30% of the cases (Fig. 7). The mutations are situated either at intracellularly faced positions (e.g. I1160V, Ptacek et
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al., 1994; V1589M, Heine et al., 1993) potentially involved in the formation of the docking site for the inactivation gate or its hinge (G1306A/V/E, Lerche et al., 1993; Mitrovic et al., 1995) which is situated in the vicinity of the IFM particle (Fig. 8). This may explain the electrophysiological finding of a combined pattern showing a small persistent current and a mildly to moderately slowed current decay (Fig. 9A).

In PC, there are 12 known mutations in 4 of the 24 exons of SCN4A accounting for approximately 50% of the patients (Fig. 7). The mutations cause a slowed current decay, a small persistent current (Fig. 9B), and an acceleration of recovery from inactivation. The slowing is most likely caused by an impaired movement of the inactivation gate itself (i.e. the intracellular loop connecting domains III and IV) or by a disturbed formation of the docking site of the IFM inactivation particle (Fig. 8), since the mutations are predominantly situated either in the inactivation gate (T1313M, McClatchey et al., 1992) or 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) which is moving outward (Yang et al., 1996) thereby presumably initiating the formation of the docking site. For one of the mutations (R1448P), slowing of the formation of a receptor site could be demonstrated

Fig. 7. Membrane topology model of the voltage-gated sodium channel of skeletal muscle. The α subunit functions as ion-conducting channel and consists of four highly homologous domains (repeats I-IV) containing six transmembrane segments each (S1-S6). The S6 transmembrane segments and the S5-S6 loops form the ion selective pore, and the S4 segments contain positively charged residues conferring voltage dependence to the protein. The repeats are connected by intracellular loops; one of them, the III-IV linker, contains the supposed inactivation particle of the channel. When inserted in the membrane, the four repeats of the protein fold to generate a central pore as schematically indicated on the right-hand bottom of the figure. The different symbols used for the known mutations leading to potassium-aggravated myotonia, paramyotonia congenita or two types of periodic paralysis are explained on the left-hand bottom. Conventional I-letter abbreviations were used for replaced amino acids.
using an inactivation gate peptide (Peter et al., 1999). Strong slowing of the current decay, which is particularly observed for PC-causing mutations, may explain the paradoxical myotonia, since in this case, the abnormal, depolarising sodium inward current flows during the action potential, i.e. with increasing exercise (Lerche et al., 1996; Mitrovic et al., 1999).

In HyperPP, there are 7 mutations known in 4 of the 24 exons of SCN4A causative in half of the cases (Fig. 7). The mutations are situated at several disseminated intracellularly faced positions (e.g. T704M, Ptacek et al., 1991; M1592V, Rojas et al., 1991) potentially involved in generating parts of the inactivation apparatus, especially the docking site for the inactivation particle. Any malformation may reduce the affinity between the “latch bar and the catch” (Fig. 8). The mutations disturb fast and slow channel inactivation and produce a long-lasting persistent sodium current (Lehmann-Horn et al., 1987a, 1991; Cannon et al., 1991; Cannon and Strittmatter, 1993; Cummins et al., 1993; Cummins and Sigworth, 1996; Hayward et al., 1997; Rojas et al., 1999). Whereas fast inactivation occurs within millis and terminates the action potential, slow inactivation acts on a time scale of seconds. When both processes are disturbed, which is only found for

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**Fig. 8. Hinged-lid model of fast inactivation of sodium channels.** Bird’s eye view of the channel consisting of four similar repeats (I to IV). The channel is shown cut and spread open between repeats I and IV to allow a view of the intracellular loop between repeats III and IV. The loop acts as the inactivation gate whose hinge GG (a pair of glycines) allows it to swing between two positions, i.e. the open channel state and the inactivated closed state where the inactivation particle IFM (the amino acids isoleucine, phenylalanine and methionine) binds to its acceptor. Various substitutions of one of the two glycines cause potassium-aggravated myotonia of different clinical severity (G1306A, myotonia fluctuans; G1306V, moderate myotonia; G1306E, myotonia permanens). The model also shows one of the four voltage sensors, IIS4, which moves outwardly at membrane depolarization thereby opening the channel pore. Mutations in IIS4 cause HypoPP type 2.
mutations causing HyperPP (Cummins and Siggsworth, 1996; Hayward et al., 1997), a particularly long-lasting, depolarizing sodium inward current can occur, like observed in HyperPP muscle specimens (Lehmann-Horn et al., 1987a). This finding is most probably responsible for the clinical differences of HyperPP compared to the other sodium channel disorders, since the profound and long-lasting depolarizations should increase the tendency to develop paralytic attacks.

In vitro electrophysiology and functional expression studies have shown that genetically determined defects of sodium channels underlie the depolarization. The mutant sodium channels then do not close properly and the resulting inward sodium current is associated with a slowly progressive membrane depolarization which initially, i.e. as long as the depolarization is small, further increases the membrane excitability (Lehmann-Horn et al., 1987b). A further progressing depolarization of 20–30 mV leads to complete inactivation at least of the wildtype channel population, and renders the membrane inexcitable and the muscle paralysed (Lehmann-Horn et al., 1987a). This state is also temporary, as excitability of the muscle fibers returns when, by action of the sodium/potassium pump, the membrane resting potential slowly assumes the physiological value of about –80 mV. The triggering of the myotonia by e.g. potassium, as in potassium-aggravated myotonia, is explained by the physiological depolarization which follows an elevation of serum potassium according to Nernst, thus unmasking the sodium channel inactivation defect. A direct effect of potassium on channel gating could not be observed (Wagner et al., 1997). In paramyotonia congenita, silent contractures can occur in addition to myotonic contractions as shown by extracellular recordings on excised muscle bundles by use of electrodes designed to pick up all electrical activity. Part of the slowed relaxation which followed the direct electrical stimulation and cooling were not caused by action potentials (Ricker et al., 1986). The most likely explanation is a long-lasting contracture induced by the sustained membrane depolarization the latter of which in turn blocks the generation of subsequent action potentials.

23.4. Periodic paralyses without myotonia: various cation channelopathies

23.4.1. Familial hypokalemic periodic paralysis – types 1 and 2

The clinical symptoms of the disease (MIM 170400) were well described in the 19th century. However, it was not until 1934 that hypokalemia was documented during the paralytic attacks. Although familial hypokalemic periodic paralysis is the most common of the primary periodic paralyses, its prevalence is estimated to only 1:100,000. The disease is transmitted as an autosomal dominant trait with reduced penetrance in women. The severity of the symptoms can vary greatly within a family. Severe cases present in early childhood, mild cases as late as the third decade of life or may go unrecognized. Initially, the attacks are infrequent, but after a few months or years, they increase in frequency and eventually may recur daily. An attack may range in severity from slight temporary weakness of an isolated muscle group to generalized paralysis. Paralytic attacks usually occur in the second half of the night or the early morning hours and on awakening the patient is unable to move his arms, legs or trunk. In most cases, the cranial muscles are spared. Usually, strength gradually increases as the day passes. Occasionally, the weakness lasts for several days.

The trigger for a nocturnal attack is often strenuous physical activity or a carbohydrate-rich meal on the preceding day. During the day, attacks can be provoked or worsened by high carbohydrate and high sodium intake, and by excitement. Injection of a mixture of antiphlogistics and local anesthetics can trigger a severe attack after a few hours.
Exposure to cold can induce local weakness. Slight physical activity can sometimes prevent or delay mild attacks.

During major attacks, the serum potassium decreases, though not always below the normal range, and there is urinary retention of sodium, potassium, chloride and water. The serum potassium decrease is accompanied by a parallel decrease in serum phosphorus. Oliguria, obstipation, and diaphoresis can occur during major attacks. Sinus bradycardia and ECG signs of hypokalemia (U waves) appear when the serum potassium falls below the normal range. Clinical or histopathologic signs of cardiomyopathy are absent.

Independently of the severity and frequency of the paralytic attacks, many patients develop a chronic progressive myopathy which can be very severe and disabling (Links et al., 1990). On the other hand, many patients do not recognize their permanent weakness as abnormal. This myopathy mainly affects the pelvic girdle and proximal and distal lower limb muscles. The MRI scan shows hypodense areas in the core of the hip extensor muscles and replacement of muscle by fat.

**Electrophysiologic findings in HypoPP**

EMG evidence of myotonia usually excludes the diagnosis of HypoPP. When there is no permanent weakness, the motor unit potentials are normal between the attacks; those with permanent weakness show myopathic changes and fibrillation potentials or sometimes a peculiar, so far unexplained neurogenic pattern. During a severe attack, insertional activity disappears, voluntary effort elicits few if any motor unit potentials, and the evoked CMAP is either abnormally small or absent. Intercritically, muscle fiber conduction velocity measured with surface or invasive EMG is abnormally low. This method can also be used to detect asymptomatic carriers. The invasive method is easier to perform and more sensitive, in particular in asymptomatic carriers. The median frequency of the power spectrum is also reduced (Troni et al., 1983; Zwarts et al., 1988; Van der Hoeven et al., 1994; Links and Van der Hoeven, 2000). In two studies with single fiber EMG, fiber densities were increased intercritically for older patients but not for those under 40 years of age. During an attack of one patient, there was a slight increase in jitter with several blocks indicating the failure of the muscle membrane to conduct action potentials (De Grandis et al., 1978; Bertorini et al., 1994).

The exercise test is performed with strong voluntary muscle contractions for 1–5 min. interrupted by short intervals every 15–20 s to avoid ischemia, best performed in one of the distal hand muscles like the abductor pollicis brevis or abductor digiti minimi. In any type of primary or secondary periodic paralysis, usually a greater than normal increase in CMAP amplitude or area during exercise is followed by a progressive decline of approximately 50% of maximum force over 20–40 min. after the exercise period. When the mean value +2 SD of normal controls is taken as a cut off (corresponding to 40–50% decline), the test is positive in about 80% of periodic paralysis patients. (McManis et al., 1986; Streib, 1987; Kuntzer et al., 2000). In chloride channelopathies, paramyotonia congenita or myotonic dystrophy, the test may also be abnormal, but usually shows a maximal decline directly after exercise with recovery during the exercise period which is in clear contrast to the progressive decline seen in PP (McManis et al., 1986; Streib, 1987; Sander et al., 1997). Measurement of muscle strength or torque induced by nerve stimulation is another option to characterize muscle function in periodic paralysis patients (Day et al., 2002).

23.4.1.1. Specific provocative testing for hypokalemic periodic paralysis

When the serum potassium of a patient cannot be investigated during a full-blown spontaneous attack, tests are required to establish the diagnosis of periodic paralysis and to determine its type. Because systemic provocative tests carry the risk of inducing a severe attack, they must be performed by an experienced physician and a stand-by anesthetist, and the serum potassium and glucose levels and the ECG closely monitored.Provocative tests with glucose with or without the additional use of insulin must never be done in patients who are already hypokalemic and potassium chloride must not be given to patients unless they have adequate renal and adrenal function.

The simplest systemic provocative test exploits the physiologic potency of glucose, or of glucose plus insulin, to cause hypokalemia. Oral administration of glucose, 2 g/kg body weight, in the early morning combined with 10 to 20 units of crystalline insulin, given subcutaneously, may provoke a para-
Skeletal muscle Ca\(^{2+}\) channel

Fig. 10. Subunits of the voltage-gated calcium channel. The \(\alpha_{1}\) subunit resembles \(\alpha\) of the sodium channel however the function of the various parts, e.g. the III-IV linker, may not be the same. \(\alpha_{5}\), \(\beta_{1}\) to \(\beta_{4}\), and \(\gamma\) are auxiliary subunits. Mutations shown here \(\alpha_{15}\) subunit of the skeletal muscle L-type calcium channel (=dihydropyridine receptor, DHPR) have been described for man (HypoPP, MHS5) and mice (mdg). Conventional 1-letter abbreviations are used for the replaced amino acids. The symbols indicate the diseases as explained at the bottom of the left-hand side.

Lytic attack within 2 to 3 hours. Exercise and intake of carbohydrates the evening before, increase the potency of the test. If the test is equivocal, intravenous administration of 1.5 to 3 g glucose per kg body weight over 60 minutes may provoke an attack. In cases that are difficult to diagnose, intravenous insulin in doses not exceeding 0.1 U/kg at 30 and 60 minutes during the glucose infusion may precipitate an attack. Another form of the test uses prolonged glucose loading, 50 g glucose in 150 ml water administered hourly for up to 15 hours. Paresis normally appears within 7 to 15 hours and paralysis within 12 to 16 hours. If these tests fail to induce an attack, they may be repeated after exercise and combined with salt loading (sodium chloride, 2 g orally, every hour, for a total of four doses). In general, a serum potassium level of 3.0 mM or less should be achieved. The test is positive when weakness ensues. CMAPs should be measured as well to confirm the weakness by an objective method. A negative test does not exclude the diagnosis of primary HypoPP because at times patients may be refractory.

As in HyperPP, the exercise test, which determines the amplitude of the compound action potential, or torque measurement may be used (see above). A positive test result confirms the diagnosis of a periodic paralysis and – in combination with a provocative factor – its type.

23.4.1.2. Molecular pathogenesis of hypokalemic periodic paralysis

Differentiating this disorder from HyperPP is of prognostic and therapeutic relevance. In 60% of the patients with a positive family history, one of the three known missense mutations in the \(\text{CACNA1S}\) gene, which encodes the L-type calcium channel of skeletal muscle, can be identified (Fig. 10) (Jurkat-Rott et al., 1994). In about 20% of pedigrees, one of the four known \(\text{SCN4A}\) mutations can be detected.
agents such as insulin and glucose, but do not explain the development of the depolarization itself. (Fig. 7) (Jurkat-Rott et al., 2000b; Sternberg et al., 2001). In both the calcium and the sodium channel, the mutations are located solely in the voltage sensing S4 segments of either domain 2 or domains 2 and 4 respectively (Fig. 8). (An additional base change has been reported for two families in a gene which codes for the accessory α subunit of the kv3.4/MiRP2 channel complex. Because of the genetic heterogeneity, testing of additional family members for linkage to the known loci is recommended in case of negative results.)

The mutations causing the more frequent calcium channel variant, HypoPP type 1, show similar functional consequences though their significance is unclear: a reduction of current amplitudes, slight lowering of the voltage threshold for inactivation and slowing of the rate of activation (Lapie et al., 1996; Jurkat-Rott et al., 1998; Morrill and Cannon, 1999). Since electrical muscle activity, evoked by nerve stimulation, is reduced or even absent during attacks, a failure of excitation is more likely than a failure of excitation-contraction coupling. Nevertheless, the hypokalemia-induced, large membrane depolarization observed in excised muscle fibers (Rüdel et al., 1984; Ruff, 1999) might also reduce calcium release by inactivating sarcolemmal and t-tubular sodium channels, and would explain why repolarization of the membrane by activation of ATP-sensitive potassium channels restores force.

Whereas in HyperPP the inactivated state of the sodium channel is destabilized, it is stabilized in the sodium channel variant of HypoPP type 2. Functional expression of the mutants revealed reduced current amplitudes, hyperpolarizing shifts of voltage-dependent fast and – for some mutations – slow inactivation, and a slowed recovery from the fast-inactivated state (Jurkat-Rott et al., 2000b; Struyk et al., 2000; Bendahhou et al., 2001; Kuzmenkin et al., 2002). All changes enhance channel inactivation (Fig. 8) and lead to a reduced number of sodium channels available for the generation and propagation of action potentials, i.e. the excitability of the myofibers is generally reduced (Fig. 11). In agreement with these findings, smaller and more slowly conducted action potentials were recorded in myofibers biopsied from patients carrying a sodium channel mutation (Jurkat-Rott et al., 2000b). These abnormal channel properties reduce the availability of sodium channels when HypoPP fibers are already depolarized, i.e. following infusion of triggering agents such as insulin and glucose, but do not explain the development of the depolarization itself.

23.4.2. Andersen’s syndrome – dyskalemic periodic paralysis with arrhythmia and dysmorphia

Andersen’s syndrome (not to be confused with Andersen disease, type IV glycogen storage disease) is defined as a clinical triad consisting of dyskalemic periodic paralysis, ventricular ectopy, and dysmorphic features (Tawil et al., 1994; Sansone et al., 1997). The dysmorphic features may be variable and include small stature, low-set ears, hypoplastic mandible, clinodactyly, and scoliosis. Cardiac disturbances may also show a variety of phenotypes such as prolongation of the QT interval, ventricular bigeminy, and short runs of bidirectional ventricular tachycardia. Sudden deaths in this syndrome probably due to cardiac arrest have been reported. Similarly to HypoPP, myotonia is not a feature of this syndrome. In contrast to HyperPP and HypoPP patients, the response to oral potassium is unpredictable: it improves weakness in patients with low serum potassium, in some families however, it improves arrhythmia but exacerbates episodic paralysis. During an attack, serum potassium may be high, low, or normal.

Several mutations in a voltage insensitive α subunit of a potassium channel expressed in both skeletal and cardiac muscle have been described (Plaster et al., 2001) (Fig. 12). These channels are protein tetramers each consisting of only two
membrane spanning segments (M1 and M2) and an interlinker forming the ion conducting pore. They function as inward going rectifiers, i.e. they are decisive for maintaining the resting potential (rectification) by conducting potassium ions into the cell (inward going) which enlarges the concentration gradient to the extracellular space and hyperpolarizes the cell. The mutations causing Andersen syndrome reduce this potassium current and a mutant monomer is capable of exerting a dominant negative effect on a whole tetramer corresponding to the dominant mode of transmission of the disorder (Plaster et al., 2001).

Electrophysiological findings in Andersen’s syndrome Standard needle electromyography is usually normal and does not show myotonic discharges (Sansone et al., 1997). The exercise test shows similar results as seen in HypoPP (Katz et al., 1999).

23.5. Malignant hyperthermia

23.5.1. Clinical features and pathogenesis of malignant hyperthermia

Susceptibility to malignant hyperthermia (MH) susceptibility is an autosomal dominantly transmitted predisposition of clinically inconspicuous individuals to respond with uncontrollable skeletal muscle hypermetabolism upon exposure to volatile anesthetics or depolarizing muscle relaxants (Denborough and Lovell, 1960). The triggering substances lead to an increase in the concentration of free myoplasmic calcium which is released from the sarcoplasmic reticulum calcium stores via the muscle ryanodine receptor channel (Iaizzo et al., 1988).
During an MH reaction, a massive myoplasmic calcium release is induced, leading to muscle contracture especially of the masseter, generalized rigidity, and heat production. Hypermetabolism associated with the sarcoplasmic calcium elevation upregulates glycogenolysis resulting in excess lactate production, metabolic acidosis, and hyperactivation of the oxidative cycle with increased ATP depletion, high oxygen consumption and carbon dioxide production with hypoxemia and hypercapnia. Tachycardia may be observed as an early sign. During the course of the crisis, rhabdomyolysis occurs with subsequent creatine kinase elevation, hyperkalemia potentially leading to ventricular fibrillation, and myoglobinuria with the possibility of renal failure. Hyperthermia may be a late sign in some cases. If an episode is survived, normalization of edematous muscle and creatine kinase levels occur within 10-15 days. As so-called awake episodes following heavy exercise have been reported, carriers of the trait are unsuited for military service. For diagnosis of MH susceptibility, a functional test on skeletal muscle biopsy, the in vitro contracture test (IVCT), can be performed which reveals high concordance with the genetic phenotype (Brandt et al., 1999).

In the majority of families, linkage to the gene encoding the skeletal muscle ryanodine receptor, RyR1, a calcium channel which under the control of the voltage-dependent dihydropyridine-sensitive L-type calcium channel of skeletal muscle, can be found (MacLennan et al., 1990; McCarthy et al., 1990). To date, more than 20 disease-causing point mutations in RyR1 have been identified in man, most situated in the cytoplasmic part, the foot, of the protein (Fig. 13) (for review see Jurkat-Rott et al., 2000a). The base of the homotetrameric protein, is located in the membrane of the sarcoplasmic reticulum, and forms the ion-conducting pore. Functionally, hypersensitivity of RyR1 to anesthetic triggering agents has been shown to be pathogenetically causative in functional tests of both muscle, isolated native proteins, and heterologously expressed full-length receptors (Censier et al., 1998). Therapeutically, during an anesthetic crisis, dantrolene, an RyR1 inhibitor, is very effective reducing the mortality rate from former 70% to currently 10%.

MH could be very highly heterogeneous with 5 additional chromosomal loci mapped until now. However only for one (MH susceptibility type 5) of these loci, a causative gene has been identified, CACNA1S, so that this very rare type of MH is allelic to hypokalemic periodic paralysis type 1 (HypoPP-1). In contrast to the voltage sensor mutations specific for HypoPP-1 (and HypoPP-2), the two mutations so far described for MH are situated in the myoplasmic loop connecting repeats III and IV the function of which is unknown (Fig. 10). The two mutations underline the functional link between RyR1 and the DHPR in excitation-contraction coupling (Monnier et al., 1997; Lehmann-Horn and Jurkat-Rott, 1999).
23.5.2. Functional neurophysiology and in vitro testing of malignant hyperthermia susceptibility

Susceptibility to MH itself is not associated with a primary structural myopathy or electromyographic or contractile alterations. Due also to lack of clinical symptoms under normal conditions, an MH in vitro contracture test (IVCT) for biopsied muscle bundles was developed by the European (EMHG) and North American (NAMHG) malignant hyperthermia groups (European Malignant Hyperpyrexia Group, 1984; Larach, 1989). This test requires a large fresh muscle biopsy and is therefore invasive in nature and not easily performed on children. It is based on the tendency of MH muscle to be abnormally sensitive to stimuli that induce SR calcium release. The underlying procedure in both EMHG and NAMHG test protocols is the measurement of contractures upon flooding or gradually increasing concentrations of halothane and separately of caffeine (Fig. 14). A positive reaction to a triggering agent is dependent on contracture force at concentrations below predefined thresholds for each substance. Three categories result by each test according to the European protocol, contracture under or at the thresholds of both substances is considered to be MH-susceptible (MHS), one pathologic and one normal result is classified as equivocal (MHE), and two normal reactions to both agents means not susceptible (MHN). In general, correlation between the results of these two tests is quite good and the test shows a high sensitivity (true positives, 99% for EMHG and 92–97% for NAMHG) and specificity (true negatives, 93.6% for EMHG and 53–78% for NAMHG).

In contrast to the IVCT test protocols primarily aimed at determining the clinical risk of anesthesia-related events, diagnostic testing in Japan is performed by a functional test based on the quantification of calcium-induced calcium release (CICR) in saponized muscle fibers (Kawana et al., 1992). The precision of this method and correlation to the other protocols is unknown.

Clinical electrophysiology

Standard electrophysiology in MH is normal. Following injections of caffeine, succinylcholine or halothane locally in the muscle revealed a decrease of the CMAP amplitude which correlated to in vitro testing in 9 MH patients (Eng et al., 1984). A detailed EMG study in MH susceptible pigs revealed no spontaneous activity but an increased duration of motor unit potentials (Steiss et al., 1981).

23.5.3. Central core disease: myopathy with malignant hyperthermia susceptibility

Central core disease (CCD) is a congenital myopathy often associated with skeletal anomalies (Shy and Magee, 1956). Pathognomonic is the abundance of central cores along type 1 muscle fibers. CCD is often associated with MH susceptibility (Shuaib et al., 1987), and allelic to the RyR1 gene locus of MH (Haan et al., 1990; Kausch et al., 1991). The myopathy is characterized by congenital muscle hypotonia (floppy infant syndrome), proximally pronounced weakness, delayed motor development, and slight CK elevation. In addition skeletal anomalies such as congenital hip displacement and skoliosis are frequent. Later in life, muscle strength

![Fig. 14. In vitro contracture test in muscle bundles of a malignant hyperthermia susceptible patient according to the European protocol. Upper panel: halothane. Lower panel: caffeine in increasing concentrations. After initial prestretching (peak in the curve), note the development of pathologic contractures (≥200 mN) at 2 vol.% halothane and 1.5 mM caffeine.](image-url)
usually improves except for rare cases showing progressive muscle weakness. It is one of the rare known myopathies for which strong physical exercise seems to be beneficial (Hagberg et al., 1980) although exercise-induced muscle cramps are often reported. Autosomal dominant inheritance is highly predominant and although several sporadic cases have been reported, a clear recessive trait has not yet been demonstrated. The clinical expression of the disease is highly variable. Not all mutation carriers in a family may develop this myopathy but instead may only have the MH trait (Islander et al., 1995).

Except for one mutation, all situated in the C-terminus of the RyR1 protein thought to form the channel pore region (Fig. 13). Expression of these mutations in non-muscle cells led to the finding of a leaky calcium release channel compatible with the view of a myoplastic calcium overload responsible for the mitochondrial and cell damage (Lynch et al., 1999; Tilgen et al., 2001). Recently a selective disruption of the orthograde excitation-contraction coupling process has been found in a skeletal muscle expression system suggesting a dominant negative effect of the CCD mutations on the voltage-controlled calcium release (Avila et al., 2001). This functional disruption may contribute to the muscle weakness and atrophy in the patients.

Electromyography in CCD

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