

ALTERED SODIUM CHANNEL BEHAVIOUR CAUSES MYOTONIA IN DOMINANTLY INHERITED MYOTONIA CONGENITA

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Abstract—The cause of increased excitability in autosomal dominant myotonia congenita (MyC) was studied in resealed > 3-cm long segments of muscle fibres from eight patients. Three hours after biopsy only about 50% of the fibre segments had regained a normal resting potential. This differs from our experiences with normal muscle or other disorders of myotonia (e.g. recessive generalized myotonia) where nearly all cut fibres reseal and repolarize during this time. When the depolarized MyC fibre segments were placed in a solution containing 1 μ M tetrodotoxin (TTX) they repolarized to -80 to -90 mV. In fibre segments with normal resting potential, in the absence of TTX, spontaneous myotonic runs were recorded intracellularly, occasionally with double spikes. For only one of the eight patients, the Cl^- conductance was reduced (50% of the total membrane conductance vs the usual 75%), for the rest of the patients the steady-state current-voltage relationship was normal. Sodium currents through single membrane channels were recorded with a patch clamp. For every patient re-openings of the Na^+ channels were observed throughout 10-ms depolarizing pulses. These are very uncommon in normal muscle. At potentials positive to the resting potential, the duration of the re-openings increased, but the current amplitude was the same. It is concluded that in myotonia congenita re-openings of Na^+ channels are the major cause of hyperexcitability and that Cl^- conductance is normal. If it is reduced in rare cases, it may potentiate the myotonia.

INTRODUCTION

The low-chloride conductance theory for the explanation of myotonia was first put forward by Bryant [1,2] on the basis of his studies of normal fibres bathed in Cl^- -free solution and of muscle fibres biopsied from myotonic goats. Later this theory was shown to hold also for myotonia in man [3,4] and thus gained widespread recognition as *the* explanation of the pathomechanism of myotonia [5,6]. In the past years it has been shown, however, that there are several diseases with myotonia (paramyotonia congenita [7], hyperkalemic periodic paralysis [8], Schwartz-Jampel syndrome [9], myotonic dystrophy [10]) in which the sarcolemmal chloride conductance is little changed or normal, and the alteration seems to be situated in the Na^+ channel. This seems to make it worthwhile to re-examine the situation in myotonia congenita.

In Lipicky and Bryant's early human studies [4] the distinction between Thomsen's disease, i.e. myotonia congenita with autosomal dominant inheritance, and the much later described recessive generalized myotonia [11] was not yet made. The two diseases differ, however, not only in the mode of inheritance, but also clinically [12]. Furthermore there were two unexplained cases with normal chloride conductance among Lipicky and Bryant's patients. It was therefore suggested that the pathomechanisms of these two diseases with myotonia might be different [6].

Recently it was reported that in human recessive generalized myotonia the Cl^- conductance, g_{Cl} , is abnormally low [13,14]. In the present study we have tried to answer the remaining question, i.e. to check the pathomechanisms in dominant myotonia congenita.

PATIENTS

Eight male patients from seven different families with dominantly inherited non-dystrophic

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Table 1. Case reports

Patient	Age (yr)	Affected relations	Myotonic signs and diagnosis	Other signs	Morphology/histochemistry
MyC1	22	Two brothers, mother, grandmother	Lid-lag, paradoxical eyelid myotonia, myotonic runs; cold: no effect, K ⁺ load (120 mmol) caused severe generalized myotonia "Myotonia fluctuans"	None	Subsarcolemmal vacuoles
MyC2	36	Daughter, mother	Lid-lag, percussion myotonia, slight clinical myotonia, myotonic runs, warm-up phenomenon, myotonia aggravated by cold and K ⁺ load (80 mmol) "Myotonia fluctuans"	Slight atrophy of right pectoralis major, bronchial spasms, elevated CK (200 U/l)	Focal type I atrophy
MyC3	62	Daughter, mother, grandmother great-grandmother	Percussion myotonia, clinical myotonia with warm-up, myotonic runs "Thomsen type"	Transient weakness, arm muscles poorly developed	Slight hypertrophy, type IIb deficiency
MyC4	55	?	Slight myotonia with warm-up, myotonic runs "Thomsen type"	Transient weakness, ischiadica	Type IIb deficiency
MyC5A	27	Brother (MyC5B), mother	Lid-lag, percussion myotonia, clinical myotonia, myotonic runs, elevated K ⁺ or cold: no effects "Myotonia levior"	None	Type IIa deficiency
MyC6	41	Sister, son	Lid-lag, percussion myotonia, slight clinical myotonia, myotonic runs "Thomsen type"	Hypertrophy	Slight hypertrophy
MyC5B	25	Brother (MyC5A), mother	Lid-lag, percussion myotonia, clinical myotonia, myotonic runs, elevated K ⁺ or cold: no effects "Myotonia levior"	None	Type IIa deficiency
MyC7	45	Son, sister, mother, grandfather, great-grandfather, "great-great-grandfather" = Dr Thomsen	Lid-lag, grip myotonia, warm up, myotonic runs, cold: no effect, K ⁺ load (80 mmol): no effect "Myotonia Thomsen"	Well-developed muscles	Slight myopathy (fibre splitting, central nuclei increase), type IIb deficiency, variations of diameter

myotonia gave informed consent for a thorough clinical investigation and for a muscle biopsy. In each family at least one additional family member in the generations of either the parents or offspring was identified to have myotonia. The *propositi* were chronologically numbered for easier cross-referencing with earlier publications. Detailed case reports are presented in Table 1.

Autosomal dominant myotonia congenita is clinically not homogenous [12]. The best known condition, Thomsen-type myotonia congenita, is characterized by a steady presence of myotonic symptoms that can easily be detected in a clinical examination. Exposure to cold or a potassium load does not aggravate the myotonic stiffness. To be sure to investigate the pathomechanism of "Thomsen's disease" we traced an offspring of Dr Asmus Julius Thomsen [15] and included him in this study (patient MyC7; pedigree in Ref. [17]). Three other unrelated patients with Thomsen-type myotonia congenita (MyC3, MyC4, MyC6) were also available.

DeJong [16] described a more benign form of the disease where clinical myotonia is absent. Thus, the patients are often unaware of their

condition. Myotonia can, however, always be recorded electrically and the clinical sign of lid-lag is usually present. Two brothers with this "myotonia levior" (MyC5A and MyC5B) entered our study.

Finally, a third, dominantly inherited condition was observed where in the same patients the severity of the myotonia fluctuates with time [17]. Occasionally, myotonia is clinically absent, but at times it may become very severe. A potassium load seriously aggravates the stiffness, in contrast to (what is seen in) the other two forms. Two of our patients (MyC1 and MyC2) had this "myotonia fluctuans". The cold-induced stiffness detected in patient MyC2 made it difficult to distinguish his myotonia from paramyotonia congenita.

METHODS

From each patient a muscle biopsy (fibre segments with lengths greater than 3 cm) was taken under local anaesthesia from either the biceps brachii or the vastus medialis muscles, depending on which showed more electrical myotonia. When possible, the endplate region

Table 2. Resting potentials, membrane resistance, component ion conductances, and percentage of current produced by re-openings of Na⁺ channels in muscle from patients with autosomal dominant myotonia

Patient	Myotonic runs		RMP (mV)	R_m at -80 mV (Ωcm^2)	g_K ($\mu\text{S cm}^{-2}$)	g_{Cl} ($\mu\text{S cm}^{-2}$)	g_{Cl}/g_m (%)	Late current (%)
	<i>in vivo</i>	<i>in vitro</i>						
MyC1*	+++	++	-65.8 ± 9.2 (6) -80.0 ± 6.0 (20)†	5126 ± 3005 (8)	66	214	76	‡
MyC2*	+++	-	-58.5 ± 4.4 (16)	6517 ± 3150 (6)	37	146	80	6.1 ± 0.9 (3)
MyC3	++	++	-83.8 ± 3.4 (6) -84.5 ± 4.8 (10)†	14451 ± 5764 (12)	40	40	50!	5.2 ± 0.8 (5)
MyC4	++	+	-74.4 ± 4.7 (9) -78.5 ± 6.5 (6)†	3280 ± 690 (6)	108	209	66	3.8 ± 1.4 (3)
MyC5A§	+	+	-49.5 ± 5.3 (10) -81.0 ± 6.8 (6)	6008 ± 2960 (5)	51	162	76	4.2 ± 0.9 (4)
MyC5B§	+	+	-47.8 ± 4.3 (8) -80.5 ± 6.3 (7)†	9665 ± 3674 (10)	36	77	70	‡
MyC7	+	+	-79.4 ± 3.1 (8) -73.8 ± 4.6 (6)†	7161 ± 1971 (7)	23	125	87	‡
Controls	-	-	-80.4 ± 2.1 (82)	4610 ± 937 (10)	42	175	80	< 0.1 (9)

Mean values ± S.D.

- RMP = resting membrane potential.
 R_m = membrane resistance.
 g_K = K⁺ conductance.
 g_{Cl} = Cl⁻ conductance.
 () = number of fibres or number of patches.
 / = between values.
 - = none, + = little, ++ = moderate and +++ = strong electrical myotonia
 recorded either *in vivo* or *in vitro*.
 * = myotonia fluctuans.
 † = in 1 μM tetrodotoxin.
 ‡ = no data.
 § = myotonia levior (brothers).

was included. Several fibre bundles with diameters of 2–3 mm were prepared from the biopsy for use in various experiments. All procedures were in accordance with the Helsinki convention and were approved by the Ethics Commission of the Technical University of Munich.

The standard solution used for transportation, dissection, and voltage-clamp experiments contained (in mM): NaCl 108, KCl 3.5, CaCl₂ 1.5, MgSO₄ 0.7, NaHCO₃ 26.2, NaH₂PO₄ 1.7, Na gluconate 9.6, glucose 5.5, sucrose 7.6 (315 mosmol l⁻¹). The Cl⁻-free solution used in some of the voltage-clamp experiments was made by replacing NaCl and KCl with respective methane sulfonate salts, by replacing CaCl₂ with Ca gluconate and by omitting the sugars in order to avoid hyperosmolarity. All solutions were maintained at 37°C if not indicated otherwise. The pH was adjusted to 7.4 by gassing the solutions with 95% O₂ and 5% CO₂. Some solutions contained 1 μM tetrodotoxin (TTX; Roth, Karlsruhe, F.R.G.).

Capacity-compensated microelectrodes were used to record resting and action potentials and for the three-microelectrode voltage-clamp experiments. Current–voltage relationships were recorded both in normal and in Cl⁻-free, TTX-

containing solution [7]. The latter curve was considered to represent the voltage dependence of the potassium current, the difference between the two curves was considered to represent the voltage dependence of the chloride current. The slopes of these curves then give the voltage-dependent component conductances, g_K and g_{Cl} , respectively. The conductance values given in Table 2 are those obtained for -80 mV. Data collection and analysis were simplified by the use of a Turbo AT personal computer.

For the study of Na⁺ currents on the single-channel level, bundles of fibre segments were superfused for up to 2 h with a standard solution containing 1–2 mg ml⁻¹ collagenase (Type Ia, Sigma Chemical, St. Louis, MO, U.S.A.). After this treatment, standard patch clamp techniques were employed at room temperature [18]. The Na⁺ channel activity was measured in both the inside-out and cell-attached modes. Inside-out patches were moved at the tip of the patch clamp pipette to a compartment of the recording chamber which was perfused separately. The “intracellular” solution with which the sarcoplasmic side of an inside-out patch was washed contained (in mM): KCl 150, MgCl₂ 2, Ca Cl₂ 1, EGTA 10, and HEPES 10 (pH 7.2). The patch clamp data were stored on a modified PCM

recorder (44 kHz digitization rate) and evaluated off line (Hewlett Packard 9800, Palo Alto, CA, U.S.A.). Firstly, the capacity peaks were subtracted from each trace in the usual way, then an event-detecting program was used to evaluate single-channel current. "Idealized records" were then produced by plotting the normalized events into an amplitude-time histogram, i.e. "1" was stored in the first time bin if there was one event in this time bin. The idealized records show immediately how many channels are open at a given time after the start of the depolarizing step. Averaging of such records yields the mean number of open channels as a function of time after the beginning of the depolarization step [19]. All pooled values given in Table 2 are mean values \pm S.D. Statistical differences for multiple comparisons were determined by Scheffe's multiple contrast test (non-parametric).

RESULTS

Resting potentials

In the standard solution about 50% of the fibre segments from the myotonia congenita patients did not regain a normal resting membrane potential (see Table 2). This is in contrast to our experience with fibre segments from normal muscle or those from patients with various other myotonic disorders [20]. When placed in TTX, the depolarized fibres quickly assumed normal resting potentials, when TTX

was subsequently removed, they depolarized again. Myotonic runs could only be recorded from fibre segments with high resting potential. This electrical activity was totally blocked by 1 μ M TTX.

Action potentials

The myotonic runs either occurred spontaneously or were induced by the penetrating microelectrode. By impaling a fibre segment at different sites we found that the action potentials were propagated with approximately the same amplitude along the whole fibre segment. At the beginning of a myotonic run, firing occurred at a regular high frequency. Subsequently, as the baseline of the spikes slowly decreased, the action potentials became smaller and wider. Quite often fibre segments repolarized spontaneously and subsequently myotonic activity restarted (Fig. 1). This behaviour was similar to that seen in fibres from patients with recessive generalized myotonia [12], myotonic dystrophy [10] and Schwartz-Jampel syndrome [9].

Current-voltage relationships

In seven out of eight patients, the current-voltage relationship had a normal slope reflecting a normal membrane conductance, g_m (Fig. 2). In one patient, the slope was smaller than normal and analysis with Cl^- -free solution showed that g_k was normal while g_{Cl} was reduced. The mean

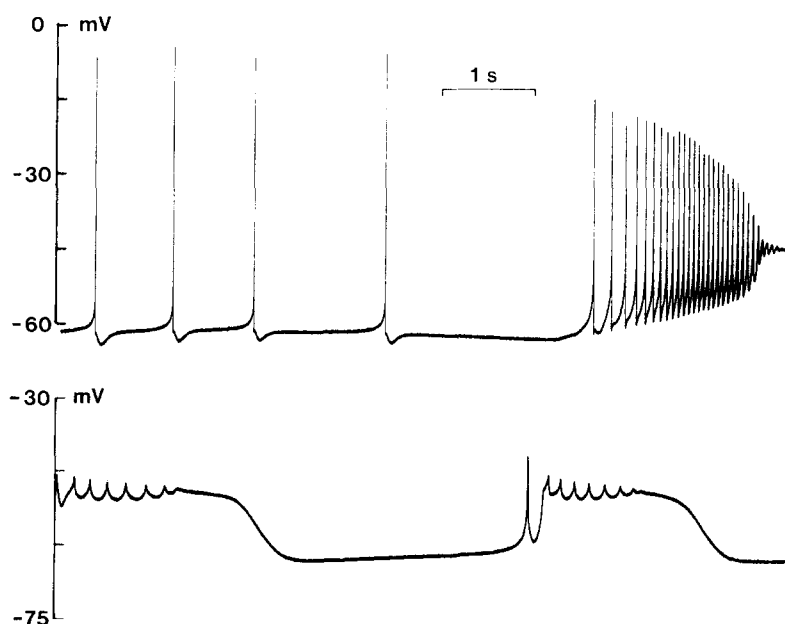


Fig. 1. Myotonic runs recorded intracellularly from a resealed fibre segment from patient MyC3. Note the spontaneous repolarization of the fibre segment at the end of each run.

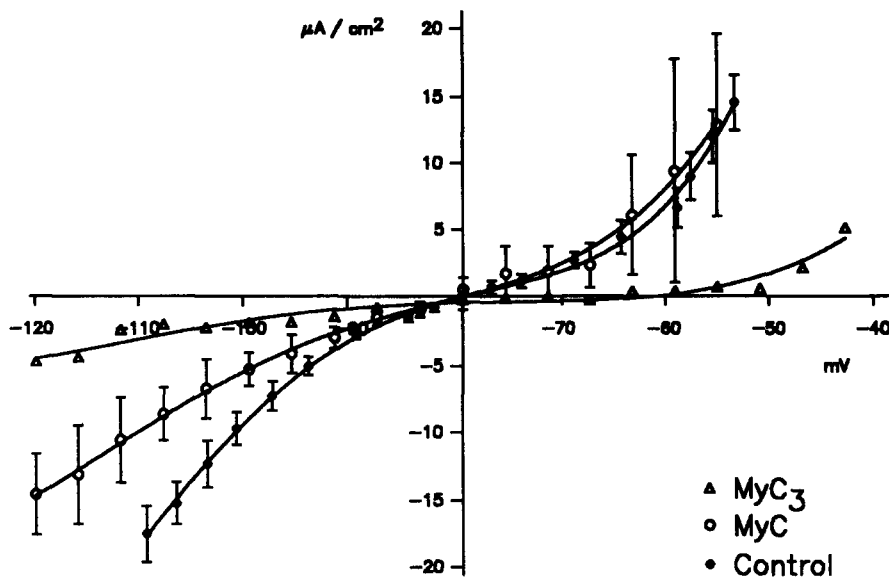


Fig. 2. Current-voltage relationships determined in resealed fibre segments from seven different patients with autosomal dominant myotonia congenita. In the standard solution, the averaged curve for the patients (○) was the same as for normal controls (●), except for patient MyC3 (Δ), where the slope of the curve was decreased indicating a reduced Cl⁻ conductance.

K⁺ and Cl⁻ conductance values for each patient are listed in Table 2.

Patch clamp experiments

Measurement of Na⁺ currents through single-channels in the cell-attached mode showed that immediately after the beginning of a depolarizing voltage step several channels opened (Fig. 3). Such early openings were always seen, in patches both from patients and from controls. But, in contrast to controls, patches from patients showed a high rate of late openings (occurring later than 10 ms after the beginning of the pulse). The amplitude of the single-channels current was the same for late and early openings. Macroscopic Na⁺ currents were reconstructed by averaging about 100 responses to the same depolarizing step (not shown). The time constant of the decay of the macroscopic Na⁺ currents, τ_h , was voltage-dependent and did not differ from controls.

To quantify the proportion of late current, we produced "idealized records" as described in the Methods section. If these records are averaged, the mean number of late openings can be evaluated. Figure 4 illustrates averaged data from one patch, obtained with two depolarizing pulses of different amplitude. The rate of late openings given in Table 2 was calculated by dividing the mean number of late openings by the number of openings in the peak of the early current.

DISCUSSION

The major finding of this study is that in seven of our eight patients with dominantly inherited myotonia congenita, the chloride conductance of the sarcolemma was normal. This is remarkable because following the pioneering experiments of Bryant with myotonic goats [1], and of Lipicky and Bryant with external intercostal muscle from human myotonic patients [3,4], it was generally assumed that the low-chloride conductance pathomechanism applies to human dominantly inherited myotonia congenita. In fact, however, Lipicky and Bryant reported that four of their six original patients had reduced g_{Cl} , while two had normal g_{Cl} [4]. Later, Lipicky reported that in five further myotonic patients g_{Cl} was again reduced [3]. Since in these reports there was no mention about the mode of inheritance, it might be fair to suggest that of these eleven patients only two with high g_{Cl} had dominantly inherited myotonia congenita, while the nine patients with reduced g_{Cl} were in fact cases of recessive generalized myotonia. For it was shown that the low-chloride theory of myotonia holds in the latter disease. Moreover, it is indeed much more common than the former. We therefore contend that, in addition to the well-known low-chloride conductance mechanism of myotonia, there exists at least one other pathomechanism, which is relevant in dominantly inherited human myo-

Dominant Myotonia Congenita (Thomsen)

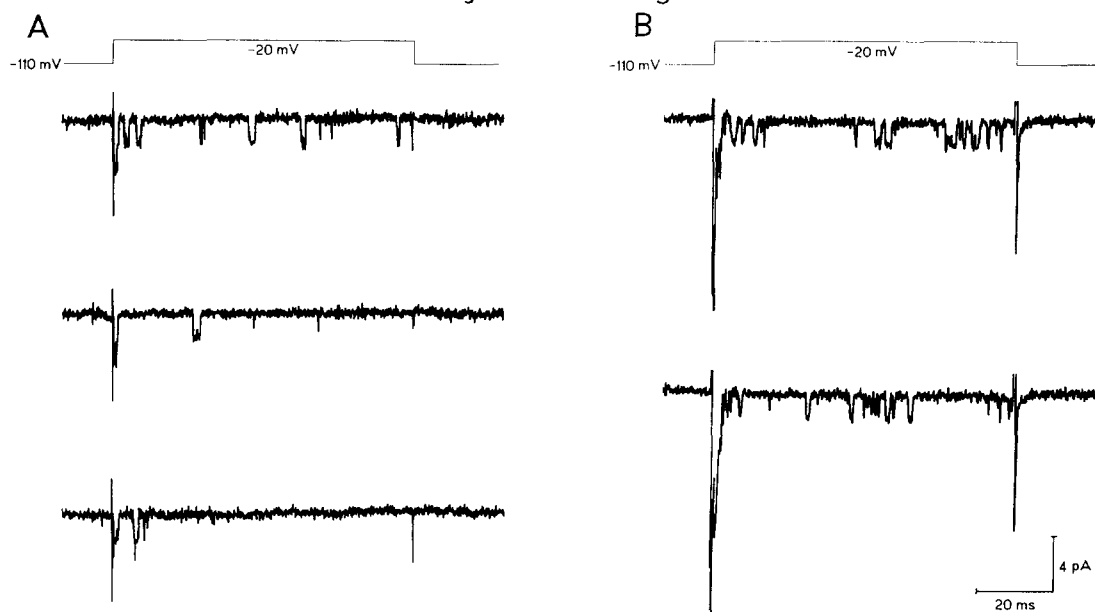


Fig. 3. Recordings from inside-out patches of muscle fibres from patient MyC4 (A) and MyC3 (B). Na⁺ channels were activated by depolarizing voltage pulses from -110 to -20 mV. Cut-off filter at 1.5 kHz.

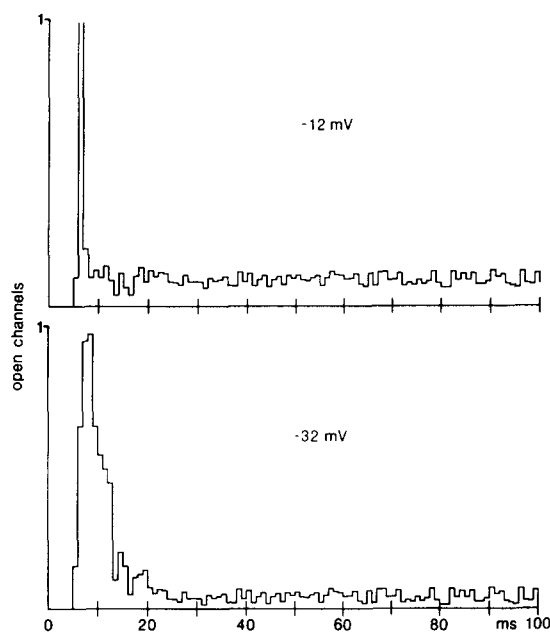


Fig. 4. Evaluation of late sodium current by averaging of idealized traces. The current was recorded from a patch of a muscle fibre from patient MyC3. Sodium channels were activated by depolarizing pulses to -12 and -32 mV. For details see text.

tonia congenita. Fortunately, we had the opportunity to biopsy Dr Thomsen's great-great grandson, who, having pronounced clinical myotonia, showed no indication of a reduced chloride conductance. Thus, we have no doubt

that in Thomsen-type myotonia congenita the low-chloride conductance pathomechanism alone does not apply.

Altered gating of the Na⁺ channel, similar to what we described here for myotonia congenita, was reported for a number of other human diseases with myotonia: the rate of late openings was increased in recessive generalized myotonia [12], myotonic dystrophy [10], and Schwartz-Jampel syndrome [9]. An alteration of the Na⁺ currents was also reported by the myotonic goat, the paradigm case of low-chloride conductance myotonia [21]. So far we have been unable to characterize the late openings to the extent that we can differentiate between the different myotonic diseases, but it seems that in recessive generalized myotonia and in myotonia congenita the rate of late openings is greater than in myotonic dystrophy. Characteristic for Schwartz-Jampel syndrome is that late openings of several Na⁺ channels in one patch occur in synchrony [9]. We found no clear-cut correlation between the amount of myotonia recorded *in vitro* and *in vivo* and the rate of late openings measured with the patch clamp technique.

In myotonia congenita the amplitudes of the single-channel currents of late openings were identical to those of the controls. In contrast, membrane patches of muscle fibres from patients with hyperkalemic periodic paralysis contained non-inactivating Na⁺ channels with altered single-channel conductance amplitudes [22].

A non-inactivating Na⁺ current was found to be the reason for the myotonia observed in patients of certain families with hyperkalemic periodic paralysis at the beginning of an attack of paralysis [8,9] and there is evidence that the genetic defect in this disease is in the gene coding for the α -subunit of the adult muscle sodium channel [23, 24]. Possibly another mutation of the same gene is responsible for dominantly inherited myotonia congenita.

In conclusion, we find that in all human diseases with myotonia the gating of the sarcolemmal Na⁺ channels is unphysiological. The altered gating produces hyperexcitability of the muscle fibres. When a certain proportion of channels does not properly inactivate, local currents may depolarize the membrane and elicit a myotonic run of action potentials. In some myotonic diseases, a reduced Cl⁻ conductance can support this process, but does not seem to be essential. Possibly, a secondary change of the membrane lipid composition is involved in the combination of the two defects [25].

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