

Intact muscle fibers or resealed fiber segments from 7 patients with recessive generalized myotonia were studied in vitro. All fibers had normal resting membrane potentials and normal resting $[Ca^{2+}]_i$ several hours after removal. Contractions were characterized by slowed relaxation which was due to electrical after-activity. Often spontaneous depolarizations were recorded intracellularly. In all fibers, the steady state voltage-current relationship was abnormal, due to a reduced Cl^- conductance. However, this conductance ranged from 0% to 66% of the total membrane conductance, whereas, in normal muscle, it was 80%. Theoretically, myotonic after-discharges would not appear until the Cl^- conductance is below 20%. Thus, the membrane hyperexcitability must be due to another defect, at least in the preparations in which the Cl^- conductance was only slightly reduced. In all patches from all patients investigated with the patch clamp technique, we observed reopenings of the Na^+ channels throughout depolarizing pulses (such behavior was absent in normal muscle). If a patch was polarized to potentials less negative than the resting potential, the duration of the reopenings increased. We conclude that a combination of reduced Cl^- conductance and the reopenings of Na^+ channels underlie the electrical after-activity in recessive generalized myotonia.

Key words: resealed fiber segments • patch clamp • 3-electrode voltage clamp • resting $[Ca^{2+}]_i$ • electromyography • myotonic runs • action potentials • force

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ALTERED Na^+ CHANNEL ACTIVITY AND REDUCED Cl^- CONDUCTANCE CAUSE HYPEREXCITABILITY IN RECESSIVE GENERALIZED MYOTONIA (BECKER)

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The recessive generalized myotonia (Becker) is clinically similar to the autosomal dominantly inherited myotonia congenita (Thomsen's disease). Unfortunately, many classifications of myotonic

disorders continue to lump together the Becker myotonia and Thomsen myotonia within the same subgroup labeled "myotonia congenita." To the contrary, the Becker type is not congenital but has its onset between the 5th and 15th year of age. In addition, Becker myotonia is more pronounced than the Thomsen type; in Becker myotonia, hyperexcitability can be detected in all skeletal muscles.³⁰ Furthermore, only in Becker myotonia are the arm and shoulder muscles found to be poorly developed relative to the hypertrophic leg muscles.³⁰

The basis of myotonia is hyperexcitability of the surface membrane of a muscle fiber. Reported abnormalities associated with hyperexcitability have included: (1) a reduced membrane Cl^- conductance in the skeletal muscle of myotonic goats,^{3,4} and in patients with various myotonic disorders^{11,21,26,27,31}; (2) an altered Na^+ current in hyperkalemic paralysis,^{22,25} paramyotonia,²⁴ in prep-

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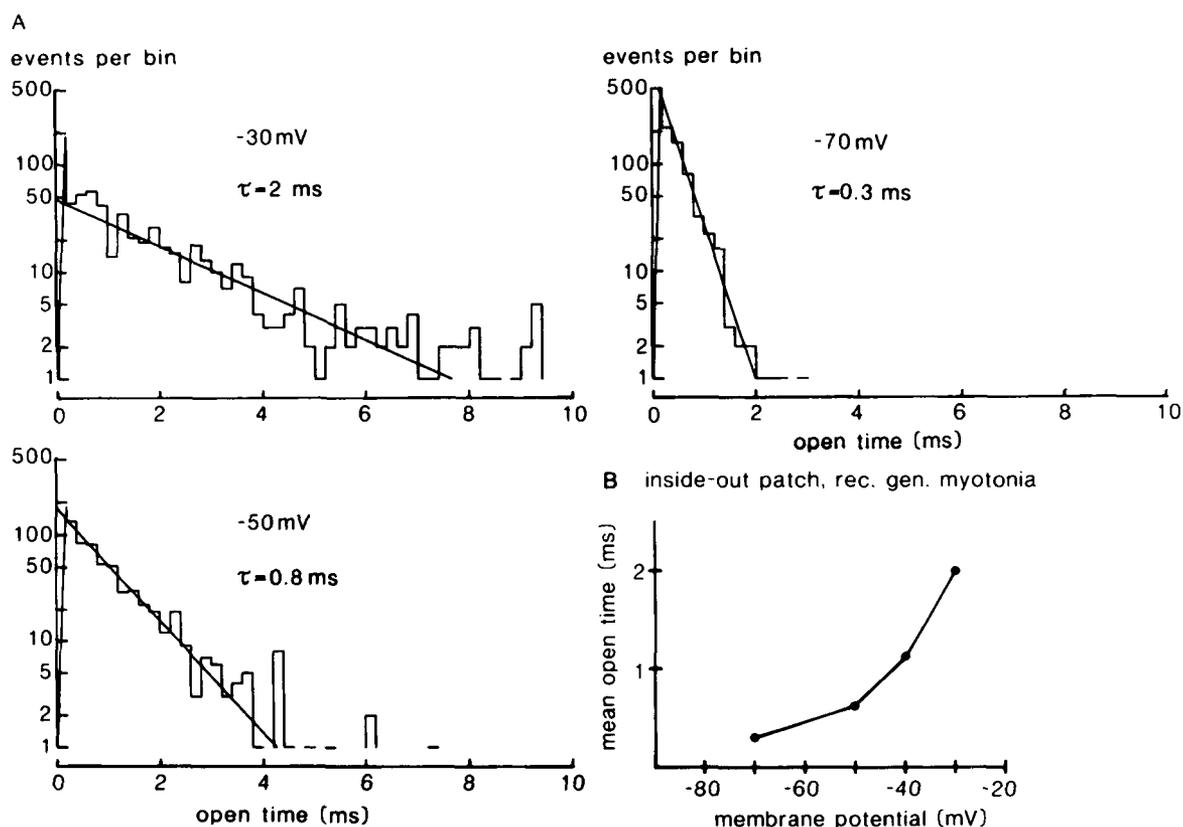


FIGURE 6. Evaluation of mean channel open time at different membrane potentials of late openings at the same patch (RGM3). **(A)** Histograms of single channel open times, fitted with single exponentials of time constant τ . Ordinates logarithmic scaled, binwidth 100 μ s. **(B)** Dependence of mean open time on membrane potential.

tal membrane conductance to explain the generation of myotonic runs.² In addition, it was shown that myotonia can be induced chemically only if the Cl^- conductance is blocked by a drug to values below approximately 20%.¹⁸ In many myotonic syndromes, a large percentage of fibers had a normal Cl^- conductance. The basis for the hyperexcitability could not be explained by the chloride hypothesis, and the basis for hyperexcitability was mostly speculative. We have described, for both the myotonic dystrophy and the Schwartz–Jampel syndrome, that a defect of Na^+ channels may account for the hyperexcitability of fibers with normal or only slightly reduced Cl^- conductance. In these disorders, a large percentage of fibers had completely normal Cl^- conductance, but elicited extreme myotonic activity.^{11,21}

One may have predicted that, in recessive generalized myotonia, more than one abnormality of the sarcolemma must be responsible for the hyperexcitability that one can record *in vivo*, extracellularly *in vitro*, or intracellularly *in vitro*. In the present study, we report that for the fibers from

patients with recessive generalized myotonia, the inactivation of Na^+ channels was abnormal and the Cl^- conductance was somewhat reduced. Both the K^+ conductance and the resting $[\text{Ca}^{2+}]_i$ were normal.

We observed that the reopening of Na^+ channels became more probable when the membrane was slightly depolarized. If enough channels spontaneously open, local potential changes may be produced. These openings of Na^+ channels probably produced the local potentials which were recorded intracellularly when the membrane was slightly depolarized by the repetitive activity. If the membrane was further depolarized, the majority of the Na^+ channels were inactivated, and action potentials were no longer propagated.

As previously mentioned, the combined alterations of reduced Cl^- conductance and an altered Na^+ channel inactivation were found to exist in fibers obtained from patients with either myotonic dystrophy and Schwartz–Jampel syndrome. However, these changes are not mutually inclusive, and fibers have been identified where only the behav-

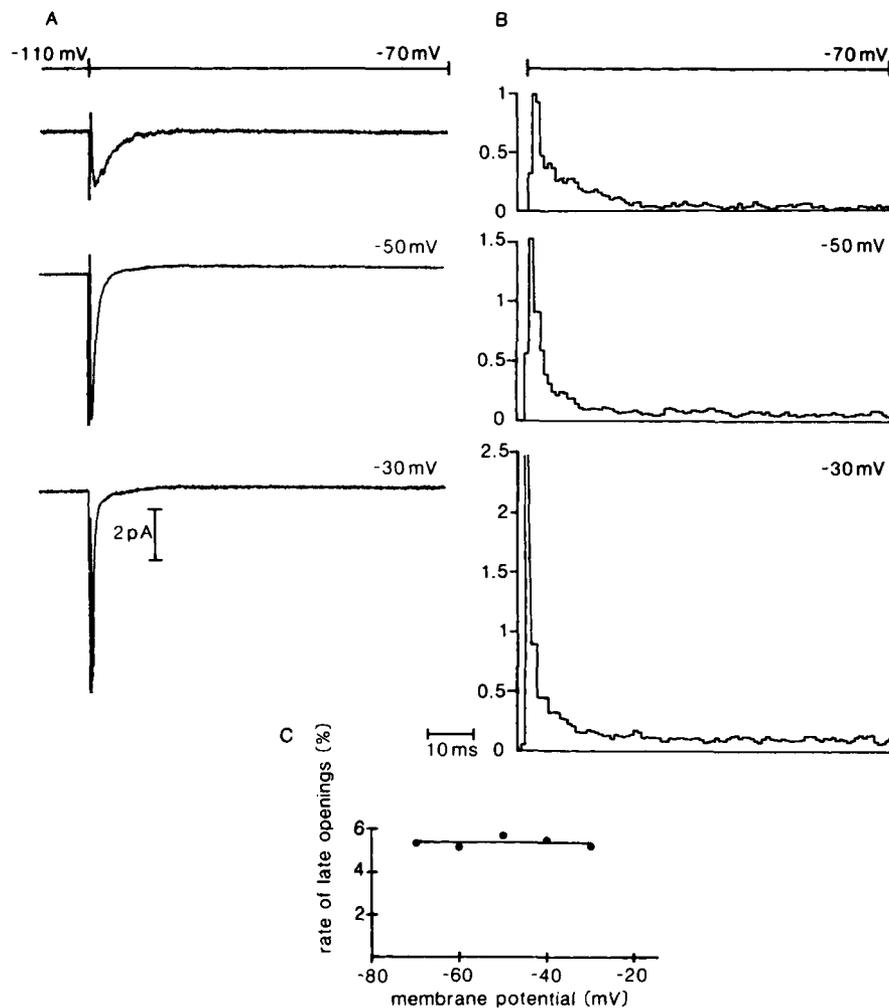


FIGURE 5. Evaluation of late Na^+ channel openings of a patch from patient RGM3. **(A)** Average of raw data. **(B)** Average of "idealized traces." The ordinate shows the number of open channels in the respective time bin, bin width 2 ms. **(C)** Rate of late current evaluated at different membrane potentials at one patch. The late current increases proportionally to the early current, resulting in a constant rate at all potentials.

Figure 6 an example of an evaluation of late Na^+ channels openings is shown for patches of myotonic muscle. The mean open time of the late Na^+ channels on the myotonic fibers was also dependent on the potential, and increased from 0.3 ms at -70 mV to 2 ms at -30 mV in the example shown in Figure 6. This increase could be observed in all 3 patches evaluated from patient RGM3.

In 1 patient (RGM7), we recorded in the cell-attached mode. The rate of late openings was increased to 0.92%. However, the rate of late openings was lower in the cell-attached mode compared with the inside-out mode in other patients (see Table 1).

Myoplasmic $[\text{Ca}^{2+}]_i$. The mean fluorescence ratios were determined for fiber segments from 2 differ-

ent patients; they were: 0.056 ± 0.007 (mean \pm SD; $n = 19$) for patient RGM6, and 0.055 ± 0.004 ($n = 30$) for patient RGM7. According to our calibration,¹⁵ this ratio corresponds to an $[\text{Ca}^{2+}]_i$ of $0.10 \mu\text{mol/L}$. The fluorescence ratios and this value for $[\text{Ca}^{2+}]_i$ were not statistically different from the corresponding values previously reported for normal muscle, which were: 0.052 ± 0.010 ($n = 212$) and $0.10 \mu\text{mol/L}$, respectively ($P \geq 0.25$).¹⁷

DISCUSSION

It was previously considered that the primary alteration within the sarcolemma, which leads to myotonia, is a decreased Cl^- conductance.^{4,5,7,12,30,31} However, it has been predicted that the Cl^- conductance has to be reduced to below 20% of the to-

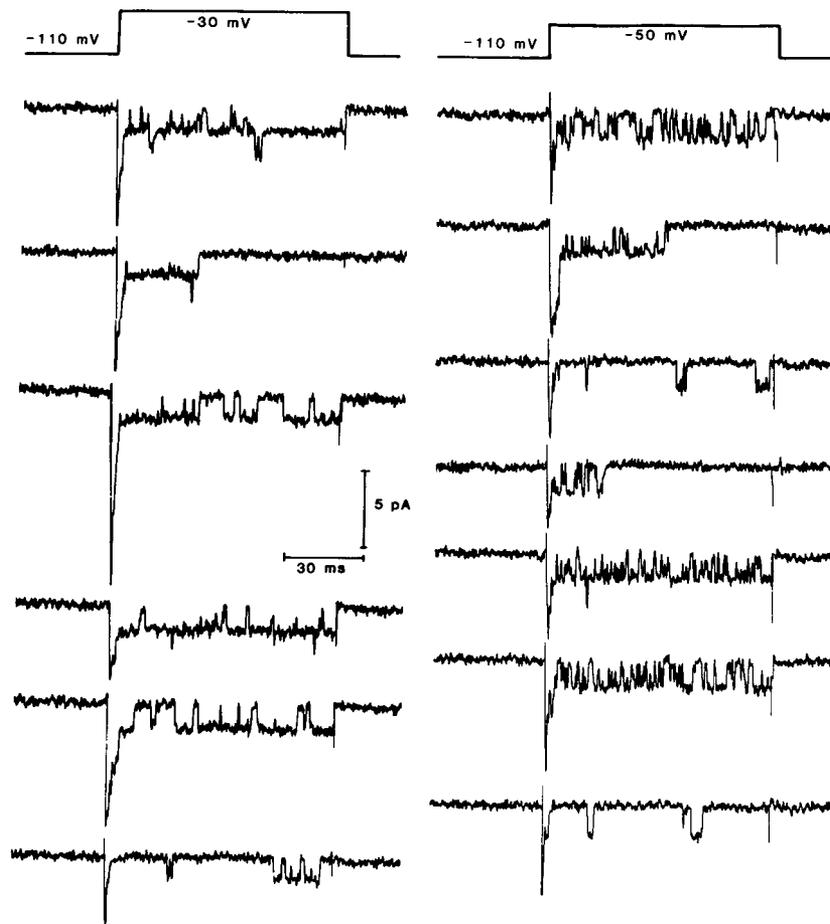


FIGURE 4. Recordings of an inside-out patch of a muscle fiber from a patient with recessive generalized myotonia (RGM3). Na^+ channels were activated by depolarizing voltage pulses of different amplitudes from a holding potential of -110 mV to either -30 or -50 mV. Traces without late Na^+ channel openings are not shown here and were more frequent at -30 mV.

tion of the late openings were greater with the larger depolarizing step.

In Figure 5A, macroscopic Na^+ currents, I_{Na} , were reconstructed by averaging numerous depolarization steps. The amplitude and the time constant of rapid decay τ_h of I_{Na} were voltage dependent. The τ_h decreased from 12.4 ms (-70 mV) to 1.2 ms at -30 mV in the experiment shown in Figure 5A. Similar values were found in all experiments evaluated in this way from patients and in controls.⁹

We evaluated the late openings that occurred in each depolarization step, produced "idealized records," and averaged them (Fig. 5B). The "idealized records" were produced by a computer program which detected late openings (see Methods section). The evaluated traces were stored and averaged. In these averaged records, the amplitude of the late current could now be detected and

quantified. The late currents cannot be observed in the macroscopic current of Figure 5A, because the amplitude of the late current is only a slight percentage of the peak of the early current. There was a proportional increase in both the amplitude of the early current and the late current when the depolarization step was larger (Fig. 5B). We then calculated the ratio of late current to early current. To calculate this ratio, the peak amplitude of I_{Na} and the mean amplitude of the current produced by the late openings were used. This ratio remained the same for all potentials (Fig. 5C). A comparison of these values is provided in Table 1 for the patches of control and of myotonic muscle.

It was previously shown that in inside-out patches of control muscle fibers, the mean open time of the Na^+ channels increased if the patch was depolarized to more positive values.⁹ In Fig-

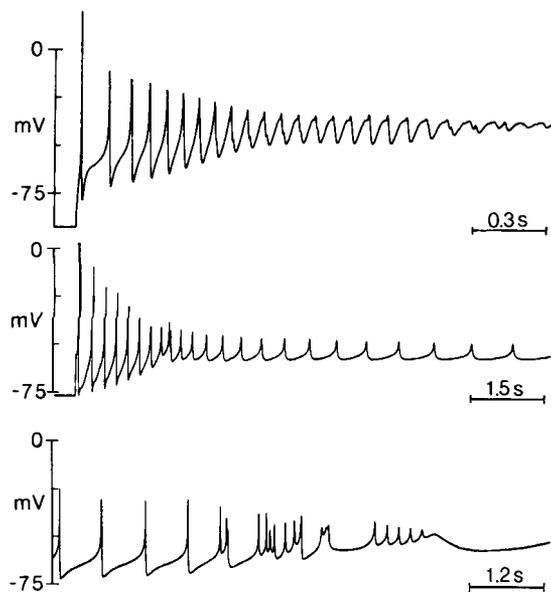


FIGURE 2. Intracellular recordings of action potentials of 3 different resealed fiber segments of a patient with recessive generalized myotonia (RGMy5). The upper two traces show the beginning of spontaneously occurring myotonic runs, the myotonic run shown in the lowest trace was elicited by the impaling microelectrode. Note the depolarization of the fiber during the first action potentials.

tials was the same along the fiber segment. Subsequently, the fiber membrane slowly depolarized. The width of the action potentials became prolonged until the potential eventually became multiphasic (Fig. 2).

Current–Voltage Relationship. In normal solution, the slope of the steady state current–voltage relationship reflects the membrane conductance, g_m . In addition, to calculate the ionic component conductances, the current–voltage relationships were determined in Cl^- -free solution which contained TTX. The slope of the current–voltage relationship, determined in this solution, reflects the K^+ conductance, g_K , which was normal: a slight increase of the K^+ conductance was noted only in the fibers of patients RGMy1 and RGMy5 (Table 1). The difference between the two curves (normal and Cl^- -free solutions) represents the voltage-dependent chloride current density which is proportional to the chloride conductance, g_{Cl} . In all patients, the current–voltage relationship had a low slope reflecting a decreased membrane conductance, g_m (Fig. 3). The resting Cl^- conductance was reduced to values between 0% and 66% of the total membrane conductance, compared with 80% for normal fibers (Table 1).

Patch Clamp Experiments. Shown in Figure 4 are selected examples of recordings made in the inside-out mode (RGMy3). As in control experiments,⁹ immediately following the beginning of a depolarization step, superpositions of openings always occurred (Fig. 4). The primary difference between the Na^+ channel activity in patches of controls and those of the myotonic muscle was in the rates of the late channel openings. The dura-

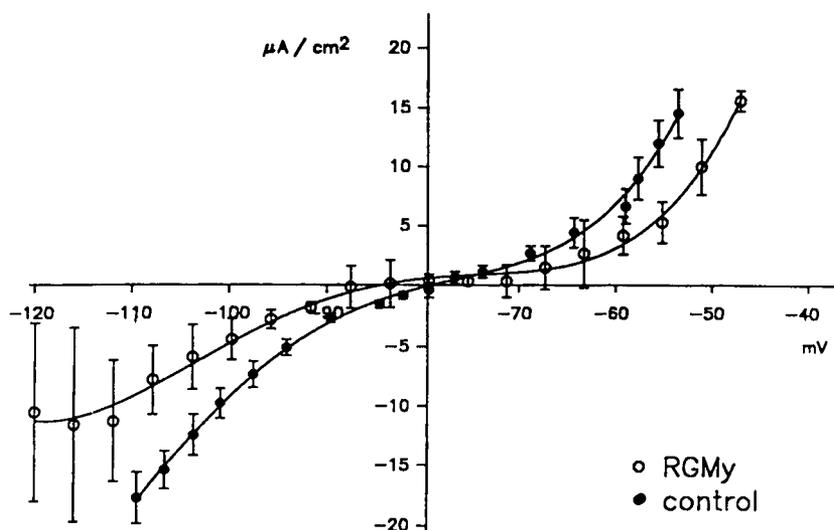


FIGURE 3. Current–voltage relationships of resealed fiber segments and intact fibers from 7 different patients with recessive generalized myotonia. In standard solution, the curve for the patients (\circ = patients) was significantly different from that obtained for normal muscle (\bullet = normal): the decreased slope of the patients' curve represented a lower Cl^- conductance. The fibers of the patients had a slightly more negative resting potential (see Table 1). The reason for the hyperpolarization is unknown.

filled with standard solution and had a resistance of 4 to 8 MΩ. After firepolishing, they had a diameter of about 1 μm. Inside-out patches were moved at the tip of the patch clamp pipette to a separate recording chamber, which was perfused separately.^{10,11} This was necessary because the collagenase-treated muscle was very sensitive to changes in the ionic composition of the bathing solution. The "intracellular" solution, with which the sarcoplasmic side of an inside-out patch was perfused, contained (in mmol/L): KCl 150; MgCl₂ 2; CaCl₂ 1; EGTA 10; HEPES 10; and the pH was 7.2.

The data were stored on a modified PCM recorder (44 kHz digitization rate) and evaluated off-line with the programs described previously.^{8,11}

After the treatment with collagenase, it was possible to obtain giga ohm seal recordings in almost all preparations. The Na⁺ channel activity was measured in the inside-out mode.

Myoplasmic [Ca²⁺]. The [Ca²⁺]_i was determined by means of the fluorescent dye fura-2. From the mean ratio of recorded fluorescence, following excitation at 340 and 380 nm, the resting [Ca²⁺]_i was estimated.¹⁶ Force was simultaneously monitored throughout.

RESULTS

EMG and Force. In either the intact fibers or the resealed fiber segments, contractions recorded in vitro were characterized by slowed relaxation which was due to electrical after-activity (Fig. 1). This behavior was identical to that recorded in vivo (not illustrated).

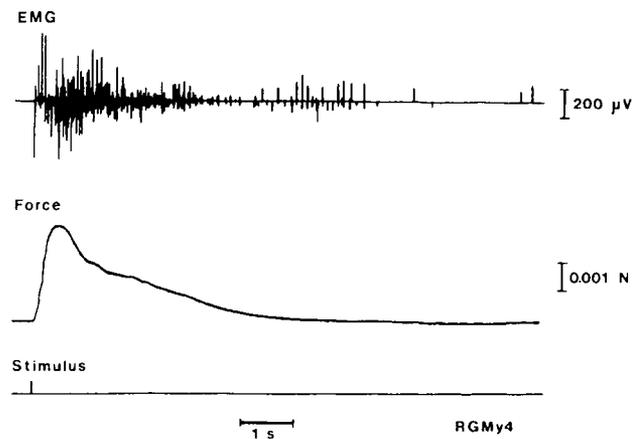


FIGURE 1. Electrical after-activity and slowed relaxation recorded in vitro. A small diameter bundle (50 to 100 fibers) of resealed fiber segments (length > 3.0 cm) obtained from a patient with recessive generalized myotonia (RGMy4) was supramaximally stimulated with a 0.1-ms pulse. Note that there was a good correlation between the extracellularly recorded electromyographic activity and the return of force to the baseline level.

Membrane Potentials (RMPs). Several hours after removal, the fiber segments had membrane potentials similar to those recorded from the intact fibers, approximately -80 mV (see Table 1). The ability to readily record myotonia in vitro is probably related to the fact that the fiber segments always had normal RMPs at the time of study (Table 1).

Myotonic runs within the single fibers occurred either spontaneously, or were induced by the impaling microelectrode. This electrical activity was totally blocked by TTX (1 μmol/L). At the begin of a myotonic burst, propagated action potentials fired repetitively. The amplitude of these poten-

Table 1. Membrane potentials, membrane conductance and current produced of patients with recessive generalized myotonia.

Patient ID	Myotonic runs		RMP (mV)	R _m (ohm.cm ²)	g _K (μS/cm ²)	g _{Cl} (μS/cm ²)	g _{Cl} /g _m (%)	Proportion of late current (%)
	In vivo	In vitro						
RGMy1	+++	+++	-81.8 ± 4.4 (21)	8630 ± 4200 (16)	71	63	47	ND
RGMy2	+++	+++	-76.1 ± 14.8 (15)	20098 ± 7365 (10)	42	14	25	ND
RGMy3	+++	ND	ND	ND	ND	ND	ND	3.9 ± 0.4 (3)
RGMy4	+++	+++	-86.1 ± 9.3 (25)	9762 ± 5164 (2)	40	79	66	4.2 ± 0.7 (3)
RGMy5	+++	+++	-80.6 ± 7.7 (18)	17046 ± 5013 (6)	63	0	0	3.6 ± 0.5 (4)
RGMy6	+++	+++	-81.9 ± 4.8 (22)	9695 ± 2780 (8)	49	60	55	4.4 ± 0.6 (4)
RGMy7	+++	+++	-77.7 ± 5.1 (12)	12634 ± 4104 (12)	41	45	52	(See text)
Controls	—	—	-80.4 ± 2.1 (82)	4610 ± 937 (10)	42	175	80	<0.1 (9)

Values given in mean ± SD.

() = Number of fibers or number of patches.

l = Between values.

- = none, + = little, ++ = moderate, +++ = strong electrical myotonia recorded either in vivo or in vitro.

ND = No data.

arations from myotonic goats,⁶ or in myoballs prepared for the various myotonic disorders³²; (3) late openings of Na⁺ channels, either random as in myotonic dystrophy,¹¹ and dominantly inherited myotonia congenita,¹⁵ or synchronized as in Schwartz–Jampel syndrome²¹; and (4) an abnormal K⁺ conductance in cultured cells derived from patients with myotonic dystrophy.^{17,27}

However, from mathematical models or experimental investigations, including some of those cited above, it has been concluded that the hyperexcitability of a myotonic muscle fiber is due to a combination of several alterations.^{1,2,11,21,30} More specifically, the mathematical models do not predict that a defect in the Cl⁻ conductance, alone, can underlie myotonic activity.^{1,2}

Hence, the present study was conducted to determine the pathogenesis of the membrane hyperexcitability in recessive generalized myotonia. A variety of techniques were used to study the electrical properties of these fibers; e.g., the behavior of single Na⁺ channel activity using both the cell-attached and inside-out patch clamp modes and the Cl⁻ conductance using the 3-electrode voltage clamp method.

PATIENTS

Seven unrelated patients, with recessive generalized myotonia, gave informed consent for in vivo investigation and for a muscle biopsy. The diagnosis of the patients was based on the typical clinical and electrical signs of myotonia, the absence of myotonia in preceding or following generations, the absence of wasting, and/or a cataract. The case reports of these patients will be given elsewhere.

From 2 patients, preparations of fibers intact from tendon to tendon were obtained from intercostal muscle. From the other 5 patients, preparations of fiber segments (lengths more than 3.0 cm) were obtained from either the biceps brachii or the vastus medialis muscles, depending on which showed more electrical myotonia in vivo. All fiber segments repolarized to normal resting membrane potentials (-80 to -90 mV) as previously reported,¹⁹ and displayed a high correlation between electrical after-activity and slowed relaxation in vitro.¹ Negative in vitro contracture tests for the determination of susceptibility to malignant hyperthermia were obtained from all preparations studied from this group of patients.²⁰ The patients were chronologically numbered for easier cross-referencing between our reports. It should be noted that patient RGMyl, in this report, was cited as patient 2 in a former study.³¹

MATERIALS AND METHODS

The specimens of intact fibers were removed under general anesthesia, whereas the specimens of fiber segments were removed under local anesthesia. When obtaining the specimens of fiber segments, attempts were made to remove samples which included the endplate region. Muscle bundles with diameters of 2 to 3 mm were prepared from all specimens and were used for the various experiments. All procedures were in accordance with the Helsinki convention and were approved by the Ethics Commission of the Technical University of Munich.

Solutions. The standard solution used for transportation, dissection, and electrophysiological experiments contained (in mmol/L): 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). The Cl⁻-free solution, used in some of the voltage clamp experiments, was made by: (1) replacing NaCl and KCl with respective methane sulfonate salts, (2) replacing CaCl₂ with Ca-gluconate, and (3) omitting the sugars in order to avoid hyperosmolarity. All solutions were maintained at 37°C, unless indicated otherwise. The pH was adjusted to 7.4 by gassing the solutions with 95% O₂ and 5% CO₂. Some solutions contained 1 μmol/L tetrodotoxin (TTX; Roth, Karlsruhe, FRG).

Electrical Membrane Properties and Force Measurements. The methods used to simultaneously monitor EMGs and force were similar to those previously described.^{14,29}

Resting membrane potentials (RMPs) were recorded with microelectrodes from surface fibers. Capacity-compensated microelectrodes were used in the voltage clamp experiments and to record action potentials. The voltage clamp experiments were conducted with 3 microelectrodes in either normal or Cl⁻-free solutions.²³ Data collection and data analysis were simplified by use of a computer system (Digital Equipment Corp., Maynard, MA).

Patch Clamp Experiments. Bundles of fiber segments were superfused for up to 2 hours with standard solution containing 1 to 2 mg/mL collagenase (type Ia, Sigma Chemical Co., St. Louis, MO). After this treatment, the standard patch clamp technique was employed.¹³ Patch clamp pipettes were pulled with a microprocessor-driven device (DMZ puller, Zeitz, Augsburg, FRG), were

ior of Na⁺ channels appeared altered. Furthermore, we have previously shown that the behavior of Na⁺ channels in the sarcolemma of normal fibers was not altered when the Cl⁻ conductance was reduced by bathing the fibers in a known blocking agent, 9-anthracene carboxylic acid.¹¹

In addition, it should be emphasized that the abnormal inactivation or gating of the Na⁺ channels in these 3 myotonic disorders were not identical: (1) in recessive generalized myotonia, the Na⁺ channel reopenings were random and their durations were voltage dependent; (2) in myotonic dystrophy, reopenings were random, the least pronounced, and the open times or durations were similar at all membrane potentials¹²; and (3) in Schwartz–Jampel syndrome, synchronized reopenings of the Na⁺ channels were abundant.²¹

Some of these differences may be explained by the varied recording techniques: Preparations of

patients with myotonic dystrophy, and of the patient with Schwartz–Jampel syndrome, were investigated mainly in the cell-attached recording mode, whereas those of patients with recessive generalized myotonia were investigated mainly in the inside-out recording mode. Different gating behavior of Na⁺ channels in excised patches has been described for cardiocytes by Nilius.²⁸ He found that long openings occurred about 20 minutes after excision of the patch with voltage-dependent open times, and discusses that phosphorylation reactions in the cell may stabilize the inactivation process.

One may question whether or not the Na⁺ channels are the primary sites of defect within these hereditary diseases. It is not clear, and the true answer may only become available when the genetic defect in each myotonic disorder has been identified.

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