Membrane potentials, current–voltage relationships, and contractile parameters were studied in intact muscle cell bundles obtained from two patients with adynamia episodica hereditaria. In a normal extracellular medium, the cell membranes had resting potentials of about −80 mV and their current–voltage relationships were not significantly different from control curves. In contrast to normal muscles the afflicted cells were paralyzed in a medium having 6–10 mmol/liter potassium. The mechanisms of paralysis in the two specimens were different from each other. Many fibers from one patient were spontaneously active even in normal solution. In high potassium solution spontaneous activity was increased and the cells gradually depolarized to values at which excitatory sodium current is normally inactivated. This depolarization was connected with an increased sodium conductance and was reversed by the application of tetrodotoxin (TTX). The fibers from the other patient were not spontaneously active. In high potassium solution they were paralyzed at membrane potential values at which normal fibers would still contract. The reason for this paralysis was a reduced excitability.

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TWO CASES OF ADYNAMIA EPISODICA HEREDITARIA: IN VITRO INVESTIGATION OF MUSCLE CELL MEMBRANE AND CONTRACTION PARAMETERS

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The autosomal dominant disorder called *adynamia episodica hereditaria* or *hyperkalemic periodic paralysis* is characterized by episodes of muscle weakness (for a recent review see reference 6). Soon after the discovery by Gamstorp[11] of an elevated serum potassium during the paralytic attack, it was suggested that the weakness may stem from a reversible depolarization of the muscle fiber membranes.[5] This was confirmed by Creutzfeldt et al.[8] and Brooks,[4] who were able to measure the intracellular membrane potentials in situ during a normal interval and during both a spontaneous and an experimentally induced attack. Some therapeutic progress was achieved by the introduction of the diuretics acetazolamide or hydrochlorothiazide[18] as a treatment that reduces the number and severity of attacks. The molecular mechanisms that lead to depolarization and paralysis of hyperkalemic muscle cells are still a matter of speculation.[20]

Episodic attacks of muscle weakness similar to those in patients with adynamia episodica are sometimes also observed in patients with paramyotonia congenita. Moreover, episodic cold-induced muscle weakness has been described in adynamia.[18] Therefore, it has been debated whether the two diseases are distinct nosological entities at all.[9,15] Clinically, it is possible to discriminate three different forms. There are families with adynamic attacks but without any signs of myotonia during

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the attack-free interval.[3] Other families have adynamia with distinct myotonia,[7] and a third group has in addition to myotonia a very pronounced cold-induced stiffness. This last form was considered identical with paramyotonia congenita.[9] Many families with paradoxical myotonia and cold-induced stiffness investigated in Germany suffer only rarely or apparently not at all from adynamic attacks[1] and the original detailed description of paramyotonia congenita by Eulenburg[10] does not mention spontaneous attacks of adynamia. Since a voltage clamp study on excised intact muscle fibers yielded some insight into the pathomechanism of paramyotonia congenita[16] we hoped to get some better understanding of both disorders from a similar study of biopsied muscle specimens from two patients with adynamia episodica. Although we are able to present valuable information on the pathomechanism of adynamic attacks, we still feel unable to decide whether or not paramyotonic and adynamic symptoms are two facets of the same disorder.

Case 1. A 17-year-old girl came to the hospital in 1980. She reported that her first episode of muscular weakness had occurred when she was 12 years of age. In the following years paralytic attacks recurred every 3–4 weeks. Muscular weakness set in after strenuous work; it could begin in either the legs or the arms and develop into generalized weakness. An episode lasted between 30 minutes and 2 hours. The weakness could be reduced by movement. The patient also reported that sometimes slight myotonic stiffness impeded her movements between attacks. She would notice such stiffness in the legs after prolonged periods of sitting, but never in the hands, not even at the beginning or during an attack of weakness. When driving a car she occasionally noticed that head and eye movements for a quick glance to the side were not at instantaneous command. She had never experienced cold-induced muscle stiffness, neither in the face nor in the hands. Once she fell into very cold water while sailing on the Atlantic Ocean. Even then her muscles did not stiffen; however, a few hours later she had an attack of adynamia. Her mother had experienced similar episodes of paralysis between ages 16 and 20, as had her grandmother between the ages of 15 and 31. The brother of the grandmother is also alleged to have had episodic weakness. No cold-induced stiffness has ever been observed in any member of the family.

The musculature of the patient was well developed, and muscle force was normal. Muscle reflexes could be easily elicited. The neurologic examination showed no abnormality. We could not detect any active myotonia in the eye or hand muscles. The thenar muscle showed percussion myotonia. Electromyographic investigation revealed myotonic runs. Unfortunately, we were not allowed to induce an attack. We are aware of an earlier test in which an oral dose of 120 mmol potassium provoked an attack of generalized weakness within 40 minutes which subsided after another 45 minutes. Determination of finger force and opening velocity[12] gave normal results when the hand and the lower arm were at room temperature. When they were cooled for 30 minutes in cold water at 15°C, muscle relaxation of a maximum isometric force exertion was not slowed, but the maximum force was decreased to 23% the amplitude at room temperature. On rewarming the maximum force recovered to 68% within 30 minutes.

Because of the absence of cold-induced stiffness we diagnosed the patient as having adynamia episodica hereditaria.

Case 2. A 47-year-old woman came to the hospital in 1981. She had experienced her first attack of episodic weakness at the age of 6 years. The attacks recurred in the following years, up to several times a week, and were usually not severe. A few times in a year, severe attacks would occur which forced the patient to stay in bed for hours. The patient's father and her 18-year-old son also suffer from a similar form of episodic paralysis. Cold-induced stiffness is not known in any member of the family. The disease was diagnosed as hyperkalemic periodic paralysis in 1974[13] and treated with acetazolamide (250 mg per day). At first the treatment resulted in a reduction of the frequency of the attacks, but after 1 year the attacks became more frequent again although the severe forms did not recur.

The patient had a normally developed musculature without atrophy or hypertrophy. The muscular force was normal except for a slight weakness during standing from the squatting position. We found no signs of percussion myotonia. Electromyographic investigation of several muscles of the patient and her son showed no myotonic runs. An oral dose of 120 mmol potassium provoked an attack of severe generalized weakness within an hour. This slowly subsided after another hour. During the attack serum potassium levels rose from 3.8 to 6.1 mM/liter. No spontaneous activity was recorded electromyographically at the onset and during the whole episode of paralysis.

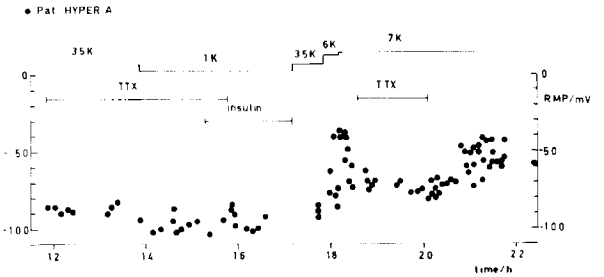

Figure 1. Resting membrane potentials recorded from fibers of one preparation from patient 1. Measurements began shortly before mid-day, 3 hours after the surgical removal of the preparation. The preparation was first bathed in the 3.5 mM potassium standard solution containing tetrodotoxin (TTX). The 1 mM potassium solution with and without TTX and with insulin caused only slight hyperpolarization. The 6 mM potassium and 7 mM potassium solutions induced strong depolarizations that could be reversed by TTX in most of the fibers.

Following the biopsy the patient was treated for 6 weeks with tocainide (Xylotocan, Astra Chemicals, Wedel/Holstein, F.R.G.), 400 mg three times a day, but the attacks recurred in unchanged form. Medication was then changed to hydrochlorothiazide (Esidrix, CIBA-Geigy, Wehr, F.R.G.), 25 mg twice a day. With this treatment, the frequency and severity of the attacks were much reduced for some weeks. However, during the following year the attacks became more frequent and severe in spite of the medication.

METHODS

The patients gave informed consent to have a biopsy specimen taken from the dorsal external intercostal muscle. The specimens were taken under general anesthesia and prepared for the measurement of membrane potentials and for voltage clamp experiments as described earlier.[16]

Contractile properties were investigated in preparations from patient 1 by recording potassium-induced depolarization contractures, and from patient 2 by recording isometric twitch contractions elicited directly by electrical pulses of 0.5 msec duration. The temperature of the bath could be quickly varied between 37°C (standard temperature) and 27°C.

Solutions. The standard solution used for transportation, dissection, and basic experiments contained (in mmol/liter): NaCl 107.7; KCl 3.48; $CaCl_2$ 1.53; $MgSO_4$ 0.69; $NaHCO_3$ 26.2; NaH_2PO_4 1.67; sodium gluconate 9.64; glucose 5.5; sucrose 7.6. The pH was set at 7.4 by gassing this solution with a mixture of 95% O_2 and 5% CO_2.

Solutions containing 1, 6, 7, and 10 mmol/liter potassium were made isomolar to the above solution by replacing the respective amount of NaCl with KCl. The chloride-free solution used in voltage clamp experiments was made by replacing NaCl and KCl by the respective methane sulfonate salts, and $CaCl_2$ by calcium gluconate.

Tetrodotoxin (TTX: Roth, Karlsruhe, F.R.G.), 0.3 mg/liter, or tubocurarine (Curarin: Asta, Bielefeld, F.R.G.), 10 mg/liter, was present in some experiments when we wanted to block sodium channels or cholinergically mediated channel activity, respectively.

The control solution for contracture experiments contained (in mmol/liter) Tris 150, potassium 4, calcium 1.5, all as propionate salts. The high potassium solution contained potassium 150 and calcium 1.5, as propionate. Solutions containing potassium at intermediate concentrations were obtained by appropriate mixture of these two solutions. When the presence of sodium was considered necessary for contracture experiments, 140 mmol/liter Tris was replaced by sodium.

RESULTS FROM PATIENT 1

During the operation, the muscles showed spontaneous twitching. Once the specimen was in vitro, twitching was terminated by the addition of TTX to the solution used for the transport to the lab (at 37°C).

Resting Potentials and Spontaneous Activity. Figure 1 illustrates the various changes in resting potential recorded from many different cells of one small fiber bundle during several tests. At the beginning, the preparation was in the standard solution containing 3.5 mmol/liter potassium. Many fibers fibrillated; therefore, we added TTX to the bath and thus stopped activity. Resting potentials were normal under these conditions (Table 1).

In an attempt to provoke a hypokalemic attack we first lowered the potassium concentration in the bath (K_e) to 1 mmol/liter. This resulted in slightly increased resting potentials, as in normal muscles. Then we added 100 IU/liter insulin (Hoechst, Frankfurt/Main, F.R.G.) to the bath (glucose was present at 5.5 mmol/liter). This had no further effect on the resting potential. When TTX was removed from the bath, occasional spontaneous activity was observed, but the resting potentials remained slightly elevated. On stimulation, the whole preparation twitched. Thus, there was no indication of hypokalemic paralysis.

To provoke a possible hyperkalemic attack, we first applied the standard solution and noticed that the resting potentials were normal again. Then we increased the K_e to 6 mmol/liter. This elicited

Table 1. Resting potentials and specific membrane conductance at respective resting potentials in two patients with adynamia episodica hereditaria and a control.*

Solutions	Patient 1	Patient 2	Normal subject IV†	E_K‡
		Resting potentials (mV)		
1 mM K	−93.4 ± 6.9 (17)	—	−96.0 ± 1.5 (6)	−132.0
3.5 mM K	−83.0 ± 4.4 (72)	−80.8 ± 4.4 (62)	−80.2 ± 2.4 (9)	− 98.5
7 mM K	−54.5 ± 10.8 (52)	−64.3 ± 9.3 (42)	−72.5 ± 4.6 (6)	− 80.0
			−67.7 ± 8.2 (16)§	
			−63.7 ± 8.0 (17)§	
7 mM K + TTX	−74.6 ± 4.4 (17)	—	−73.6 ± 2.1 (7)	− 80.0
10 mM K	—	−54.7 ± 6.1 (72)	−60.8 ± 1.8 (12)	− 70.5
			−58.6 ± 3.2 (30)§	
			−52.8 ± 7.3 (20)§	
		Membrane conductances ($\mu S/cm^2$)		
1 mM K	78 ± 14 (5)	—	77 ± 15 (6)	
3.5 mM K	150 ± 26 (8)	180 ± 49 (5)	165 ± 25 (9)	
7 mM K	154 ± 37 (6)	—	326 ± 50 (6)	
10 mM K	—	308 ± 72 (5)	298 ± 17 (5)	
3.5 mM K, Cl-free + TTX	57 ± 12 (7)	—	47 ± 6 (5)	
7 mM K, Cl-free + TTX	187 ± 59 (7)	—	222 ± 76 (4)	

*Temperature of the muscle bath was 37°C. Data represent mean values ± SD. Numbers of fibers evaluated are given in parentheses.
†Control data were obtained from subject IV. Control results from subjects I, II, and III are given in reference 16.
‡Potassium equilibrium potentials were calculated assuming K_i = 140 mmol/liter.
§Mean of values obtained from two further control subjects, V and VI.

spontaneous trains of action potentials in many fibers which, because of their low frequency and long duration, were more similar to runs observed in paramyotonia than in myotonia congenita. Figure 2 illustrates a peculiar pattern of activity that we were able to observe 3 times. From the time mark (*A*) onwards there are two potential levels from which spikes can start. After some initial irregularity, alternating starting potentials prevail (*B*). Then, the two potentials merge (*C*). From time mark (*D*) on, there exist again two distinct starting potentials that later merge again. At (*E*), the record is terminated because the microelectrode was dislodged by the movement of adjacent fibers. A possible explanation for this variable behavior may be found in the membrane characteristics of these fibers (see next section). In 15 cases we recorded only regular activity, as in the beginning of the run illustrated in Figure 2. In 46 tested fibers the resting potential was stable, and was either higher than −70 mV or lower than −60 mV. The threshold potential for regenerative electrical activity in normal intercostals is midway between these values. From these results we concluded that in 6 mM potassium solution we had established conditions favoring a transition from a normal resting potential to an abnormally low one, the latter leading to paralysis.

To reach the condition of excessive depolarization more easily, we increased K_e from 6 to 7 mmol/liter (Fig. 1). Following the change, twitching and fibrillations became stronger. Curare, when added to the bath, did not prevent this activity. A neurogenic origin for this activity can thus be excluded. After 5 minutes in 7 mM potassium, the resting potentials were low (−46 ± 10 mV) in

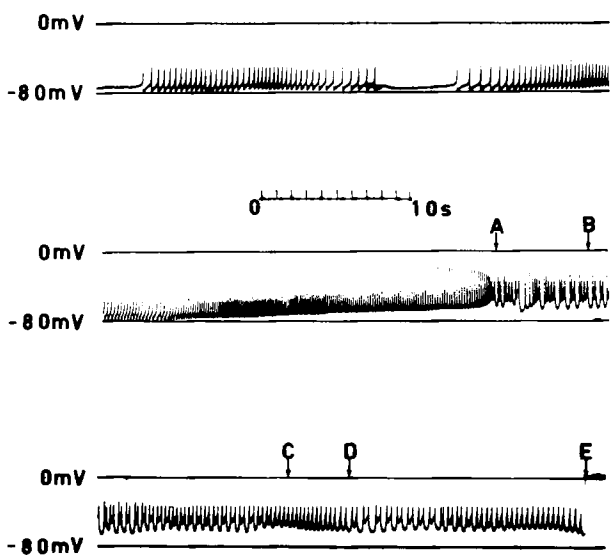

Figure 2. Intracellular recording of spontaneous electrical activity recorded in vitro in a fiber from patient 1 on elevation of the extracellular potassium from 3.5 to 7 mmol/liter. For explanation of time marks A to E see text.

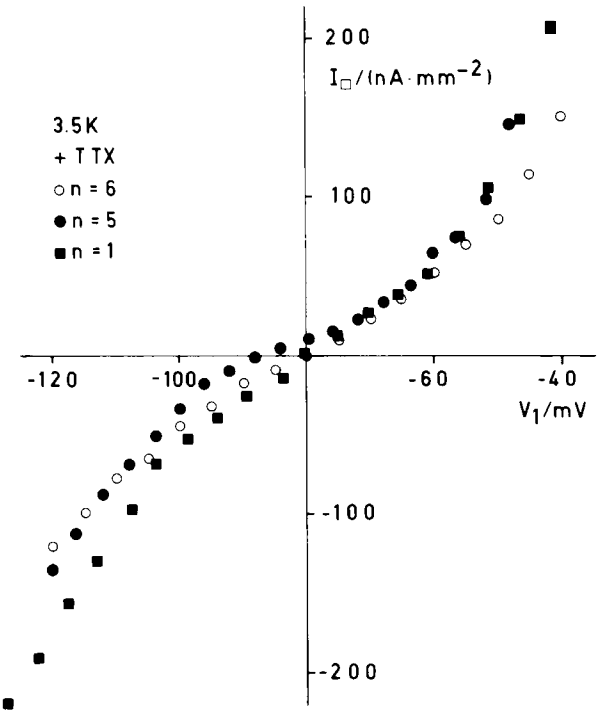

Figure 3. Steady state current density–membrane potential relationships (membrane characteristics) in the TTX-containing 3.5 mM potassium solution. Patient 1, filled circles; patient 2, filled squares; and patient 3, open circles.

seven of 10 fibers tested, and were above −70 mV (−72 ± 2 mV) in the remaining three fibers, one of which developed a spontaneous run during impalement. In a second test series performed 15 minutes later, no resting potential value above −70 mV was recorded and the mean value was −50 ± 11 mV (n = 12). The muscle fibers thus had much lower resting potentials than the −80 mV expected from the Nernst equation for K_i = 140 and K_e = 7 mmol/liter.

To test whether this depolarization was caused by increased sodium conductance (g_{Na}) we blocked the sodium channels with TTX. This caused a repolarization of the fibers to −74 ± 5 mV (n = 10, Fig. 1) indicating that indeed the depolarization in absence of TTX had been caused by an increased g_{Na}. This finding was corroborated by washing out the TTX, whereupon many fibers depolarized again. The mean resting potential remained low for the following 4 hours of observation.

Another condition for an abnormal increase of g_{Na} in fibers from patient 1 was low temperature. Intense fibrillation was provoked in the 3.5 mM potassium solution by cooling the preparation to 27°C. The fibrillation was terminated by rewarming the muscle to 37°C (not illustrated).

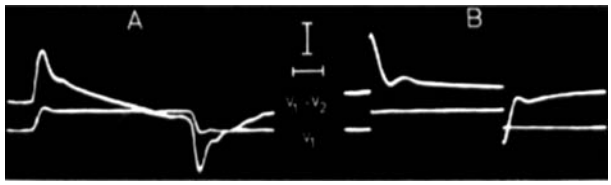

Figure 4. Membrane potential at the center electrode V_1 and potential difference V_1–V_2 during clamp pulses from −80 to −68 mV and back to −80 mV. V_1–V_2 did not attain a steady level in the fibers from patient 1 (panel A) as it did in control fibers (panel B). The preparations were bathed in standard solution. Calibration bars: 20 mV for V_1, 5 mV for V_1–V_2, 10 msec. Oscillographic records retouched to eliminate a third trace.

Membrane Conductances and Membrane Characteristics (Relationship Between Steady-State Current Density and Membrane Potential). When the measurements were made in the 3.5 mM potassium solution containing TTX we could not detect any significant difference between the membrane characteristics of muscle fibers from patient 1 and of those from normal subjects (Fig. 3).[16] When TTX was removed from the solution, the hyperpolarizing membrane currents remained normal, but for depolarizing steps from −80 to −76 mV or less no clear cut results were obtained because during the clamp pulse a depolarizing current always developed, which did not attain a steady state value. In other words, although the feedback amplifier was able to clamp the potential at the center electrode V_1, the potential at the distant electrode V_2 drifted to less negative values (Fig. 4*A*; for technical details see reference 16). With larger depolarization steps, the drift often ended in an action potential and the associated movement dislodged the microelectrodes. No depolarizing current was activated negative to −68 mV in normal fibers (Fig. 4*B*). Depolarizing (excitatory) current was seen at −64 mV and less negative potentials in normal fibers, and its threshold was well defined. Drifts such as illustrated in Figure 4*A* were never observed in normal fibers.

In 7 mM potassium solution, the characteristic curve of patient 1's fibers deviated from that of control fibers (Fig. 5). The deviation was small at the holding potential of −80 mV and became larger at less negative potentials. Between −50 mV and −40 mV, the slope conductance of the characteristic curve became negative. Similarly as in the 3.5 mM potassium solution, the clamp current did not attain a steady state value during these pulses. To indicate the nonstationary aspect of these data we have connected points by a dotted line in Figure 5. A characteristic curve having a negative slope portion that returns to the zero current axis means that the resting potential may assume two different values, the less negative one being metastable.

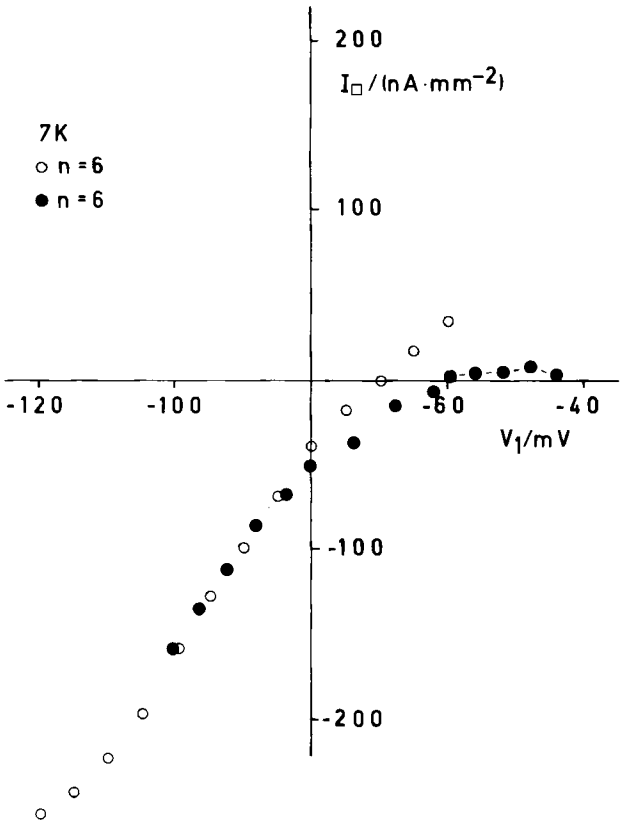

Figure 5. Membrane characteristics in TTX-free solutions containing 7 mM potassium. Results were obtained from patient 1 (filled circles) and a normal subject (open circles).

Muscle fibers having such characteristic curves are expected to tend toward spontaneous activity whereby the "resting" potential value may oscillate between two values, as actually observed (Fig. 2).

The calculated value of the resting membrane conductance in the 7 mM potassium solution was very low compared to that of fibers from the normal subject (see Table 1). On theoretical grounds, this could either mean that in the afflicted fibers all of the current components were really small or that a regenerative current component made the membrane conductance appear small. To decide between these possibilities we determined potassium component conductances (g_K) by recording membrane characteristics in chloride-free, TTX-containing 3.5 or 7 mM potassium solutions (Table 1). The g_K values of patient 1's fibers thus obtained were not smaller than normal. Therefore, the deviation of the membrane characteristic from the control seems to be caused by a regenerative sodium current component.

Contracture Experiments. Potassium contractures were carried out with five preparations. When the preparations were kept in sodium-free solution before and during potassium application they all gave contractures indistinguishable from controls.[16] The threshold potassium level, the maximum force, and the general dependence of force on the potassium concentration were normal. The ability to recover from a contracture was also normal. The effectiveness of potassium in causing contractures was less when chloride was the major anion than when chloride was replaced by propionate. This result is expected for muscles having a normal chloride component conductance.[14] The ability of the muscles to respond to potassium by contractures and to recover after a contracture was about the same at 37°C and 27°C.

When the preparations were prebathed in sodium-containing solution, the peak contracture force was one-third or less of that obtained after a prebath in sodium-free solution in four out of five preparations. The responsiveness in sodium-containing solutions could be restored to that existing in the absence of sodium by the addition of TTX to the bath. The ability to recover from a potassium contracture was highly variable in TTX-free sodium solutions. Recovery was substantial only if the recovery period was either less than 4 minutes or more than 25 minutes. An explanation for this finding may be that in solutions containing sodium, the muscle, after having recovered its contracture ability, developed spontaneous activity which caused prolonged membrane depolarization. Removal of sodium may have prevented these spontaneous excitations. In conclusion, the results from the contracture experiments with fibers from patient 1 corroborate the notion of an increased g_{Na} causing a depolarization-induced block of contraction.

RESULTS FROM PATIENT 2

Resting Potentials and Spontaneous Activity. The results obtained with muscles from patient 2 differed from those of patient 1 in many important details. During the operation no twitching of the muscles was seen. This was also true in vitro when the muscle was bathed in a 3.5 mM potassium solution. The resting potential in the 3.5 mM potassium solution was normal (Table 1). In the 7 mM potassium solution, the fibers depolarized without activity to a mean value of −65 mV, but 9 out of 42 fibers tested had resting potentials negative to −70 mV. In the 10 mM potassium solution the mean resting value was −55 mV which is 15 mV less negative than the Nernst equilibrium potential calculated for K_i = 140 and K_e = 10 mmol/liter.

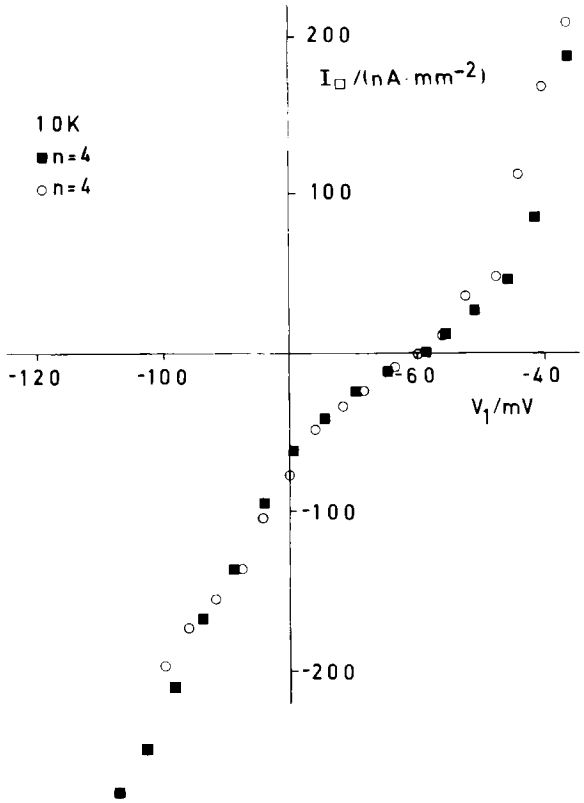

Figure 6. Membrane characteristics in TTX-free solution containing 10 mM potassium. Results were obtained from patient 2 (filled squares) and a normal subject (open circles).

Control measurements with fibers from three different normal subjects showed that the resting potentials in the 7 and 10 mM potassium solutions were very variable (Table 1). The values of patient 2 are certainly on the low side, but not outside the control range.

Membrane Characteristics. In the TTX-containing 3.5 mM potassium solution the characteristic curve obtained from one tested fiber membrane was normal (Fig. 3). In the TTX-free 3.5 mM potassium solution, four characteristic curves were recorded. They differed from control curves in that the membrane could be clamped beyond −65 mV to −45 mV before contraction artifacts made recording impossible. Excitatory sodium current was elicited during these clamp steps in the potential interval between electrical and mechanical threshold, but it seemed insufficient for an excitation leading to a strong contraction. In the 10 mM potassium solution we chose a holding potential of −60 mV. The characteristic curves of four tested fibers from patient 2 were not significantly different from control (Fig. 6).

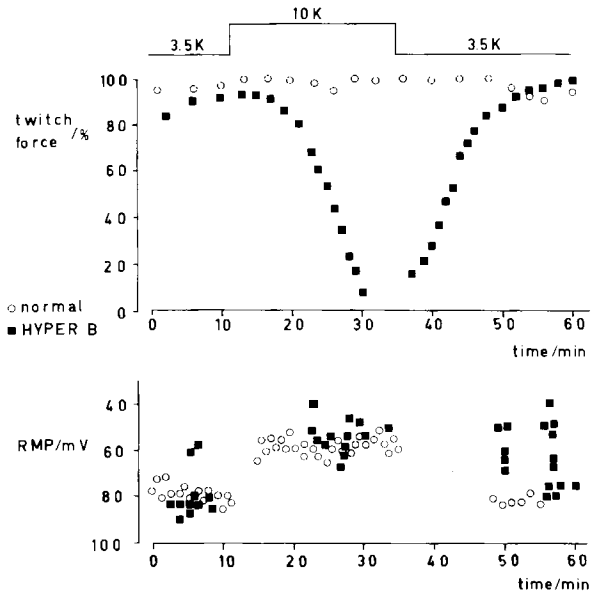

Figure 7. Twitch force and resting membrane potentials recorded from small fiber bundles of patient 2 (filled squares) and a normal subject (open circles) during a 23 minute exposure to a 10 mM potassium solution.

Contractile Properties. The ability to contract was investigated in four preparations from patient 2 by using electrical stimulation. When the potassium concentration in the bath was raised from 3.5 to 10 mmol/liter during a series of test stimuli at 1/min, the force responses quickly fell to zero. An increase in stimulus strength had no effect, showing that the loss of mechanical responsiveness was not due to a raised electrical threshold in the 10 mM potassium solution. When the potassium concentration was lowered to 3.5 mmol/liter the force recovered its full strength (Fig. 7). Tests made with five control intercostal preparations in the 10 mM potassium solution showed that normal muscles were still able to develop full force when the fiber membranes were depolarized to −60 mV. Figure 7 also shows that repolarization on readmission of the 3.5 mM potassium solution was much less complete in the afflicted fibers than in the normal ones. In spite of the persisting depolarization the preparation was able to produce force as before the test.

In two preparations from patient 2 we also tested the temperature dependence of the contraction. In the 3.5 mM potassium solution, the muscles were quickly converted from the normal to the paralyzed state and back by cooling to 27°C and warming to 37°C, respectively. In a normal control muscle the twitch force dropped by only 10% during cooling to 27°C (Fig. 8). In one preparation from patient 2 we also measured resting potentials during a cooling experiment. There appeared to

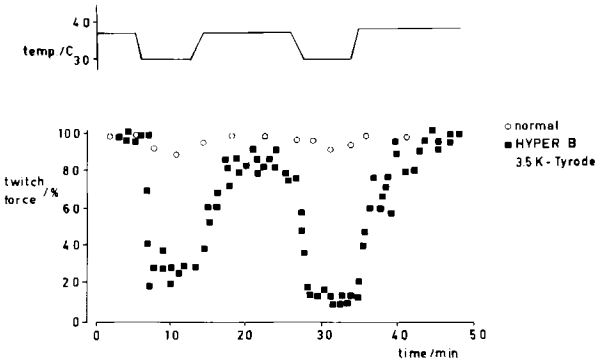

Figure 8. Twitch force recorded from small fiber bundles from patient 2 (filled squares) and a normal subject (open circles) during two periods of cooling.

be two domains of resting potential values that could be adopted, a high one between −70 mV and −85 mV, and a low one between −35 mV and −50 mV. At 37°C, 83% of the investigated fibers had resting potentials in the high domain. At 27°C, when the muscle was completely paralyzed, 60% of the resting potentials measured were still in the high domain. Therefore, paralysis in fibers from patient 2 did not seem to be connected with abnormally large membrane depolarization as in patient 1's fibers.

DISCUSSION

In this work, muscles from patients with adynamia episodica hereditaria have been subjected to electrophysiological tests in vitro for the first time. The clinical situations of attack-free interval and paralysis could be simulated by a mere increase of the extracellular potassium (K_e) from 3.5 to 7 mmol/liter, indicating that no other serum factor needs to be involved. Hyperexcitability was found in the muscle excised from one of the two patients. Spontaneous twitching did not disappear on addition of curare. It therefore seems unlikely that a change of the neuromuscular junction was responsible for this hyperexcitability.[4] Depolarizing voltage clamp steps on muscle fibers from the other patient indicated reduced excitability.

In the 3.5 mM potassium solution, the resting potentials and membrane conductances were not significantly different from those of controls. This agrees with intracellular in situ measurements of resting potentials by Brooks[4] and is in conflict with earlier results of Creutzfeldt et al.[8] and of McComas et al.[21] The discrepancy may reflect a higher inaccuracy of in situ measurements. We are convinced that all afflicted muscle fibers can assume high resting potential values. McComas et al.[21] also reported a reduced input resistance, that is, increased membrane conductance. This is not necessarily in conflict with our finding of normal membrane conductance since their fibers were depolarized to about −65 mV. When clamped to −65 mV or depolarized by high potassium solution, control fibers also had increased membrane conductance as compared to values at normal resting potential (see Table 1 and Fig. 6). Thus, our results suggest that during the attack-free interval, afflicted muscle fibers can have normal resting potentials and membrane conductances.

On elevation of K_e, the muscles from both patients were paralyzed, but there seemed to be profound differences in the mechanism of paralysis. Spontaneous activity was increased in the muscle from one patient, and the fibers depolarized to a low resting potential at which normal muscle fibers are inexcitable. This excessive depolarization was connected with an increased sodium conductance similar to the cold-induced depolarization in paramyotonia congenita.[16] There are, however, two major differences between the results obtained with this patient and those obtained with paramyotonic patients. First, the depolarization reported here was readily reversible by the addition of TTX, whereas we were never able to repolarize fibers from paramyotonic patients with TTX, not even when the fibers were rewarmed to 37°C. Second, there was no indication that in the depolarized state the chloride conductance was increased just as it was found to be in paramyotonia congenita.[16] Thus, fewer membrane parameters seemed to be altered in this particular adynamic muscle than in paramyotonic muscle, and this might be connected with the clinical experience that hyperkalemic loss of muscle strength is reversed at a faster rate than the cold-induced paramyotonic paresis. Unfortunately, we did not record membrane characteristics from adynamic muscles in the cold. The membrane characteristics of paramyotonic muscles in high potassium solution have not been studied either. A complete comparison of these in vitro results is therefore not possible.

The fibers from the other patient were also depolarized in high potassium solution, but only to a resting potential at which normal muscle fibers are excitable. The afflicted fibers, however, were paralyzed because of inexcitability. It should be noted that families have been described having hyperkalemic periodic paralysis with[7] and without[3] myotonic features. Reduced excitability in four patients with adynamia episodica was reported by McComas et al.[21] In many families no signs of hyperexcitability are reported and myotonic dis-

charges were consistently absent in the electromyograms of many patients.[2,3] The family of our patient 2[13] belongs to this latter group.

In preparations from this patient, paralysis was quickly abolished when K_e was reduced to 3.5 mmol/liter. In repeated experiments, the muscle fibers lost and regained full force in 10 and 3.5 mM potassium solutions, respectively, although most of their resting potentials did not change much on returning from 10 to 3.5 mM potassium solution. Thus, paralysis was not closely linked to depolarization in this muscle. The relatively slow and imperfect repolarization on return from 10 mM potassium to normal solution suggests that the outward, and possibly also the inward, potassium movement was reduced in these cells.[14] There was no clear evidence of a link between paralysis and depolarization when the muscle was paralyzed in the cold with many fibers still at high resting potentials. Further work will be needed to clarify this mechanism of paralysis.

The changes seen in the current–voltage relationships of the fiber membranes were not sufficient to explain all of the clinical evidence. It is possible that not only passive membrane conductances are affected in adynamia episodica but also active membrane transport mechanisms, as already suggested by Brooks.[4] Normally, the sodium/potassium ATPase is stimulated by K_e and by intracellular sodium (Na_i). It seems worthwhile to explore the assumption that in patients with adynamia episodica the pump is mainly or exclusively stimulated by Na_i. An orally administered potassium load or a potassium-rich meal would then increase K_e much more than in normal subjects[17] in which, owing to the stimulation of the pump by K_e, potassium is immediately transported into the muscle cells. The increased K_e would depolarize (and paralyze) the muscle cells. Only then would the depolarization lead to an increase of Na_i which would stimulate the pump, causing repolarization and uptake of potassium into the cells, thus leading to recovery from paralysis.

In conclusion, there seems to be more than one mechanism possible for adynamic attacks. Presence or absence of myotonic runs recorded electromyographically during an attack-free interval might be a more distinguishing feature of the disorder than recognized so far. As to the question of whether adynamia and paramyotonia are manifestations of the same disease, we would agree with McArdle's opinion[19] that "it is wise to keep an open mind until more is known about the underlying biochemical abnormalities."

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