The cause of weakness was investigated in a patient with adynamia episodica hereditaria without myotonia. A pattern of exercise and rest produced episodes of hyperkalemic periodic paralysis. In addition, local muscle weakness was induced by forearm cooling. Investigations on isolated intercostal muscle demonstrated that a high potassium concentration in the bathing solution triggered a noninactivating membrane current causing depolarization of the muscle fibers. This current was carried by sodium as it could be inhibited by tetrodotoxin. The abnormal sodium conductance led to an increase of sodium within the fibers. This was demonstrated directly by intracellular recordings. Weakness induced by rest after exercise and cold-induced weakness appeared to have different pathomechanisms. In the cold, the muscle fibers retained a normal resting potential, but their excitability was reduced and their mechanical threshold was increased. These findings also provide evidence that the mechanism of cold-induced weakness in adynamia episodica is distinctly different from the cold-induced weakness that occurs in paramyotonia congenita.
Key words: adynamia episodica hereditaria • hyperkalemic periodic paralysis • cold-induced weakness • sodium conductance

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ADYNAMIA EPISODICA HEREDITARIA: WHAT CAUSES THE WEAKNESS?

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Adynamia episodica hereditaria is a dominantly inherited disease characterized by episodic attacks of generalized weakness. During such attacks the level of the serum potassium is usually elevated (>5 m*M*). However, local weakness can also occur without a detectable change in serum potassium. The patients never develop weakness during muscle exercise even though the serum potassium increases as a physiological consequence of the muscular work. Rather the weakness develops during rest, in particular, if rest has been preceded by hard work. In addition, when the muscles of these patients are exposed to the cold, a subsequent weakness is evident.

Soon after the first description of the disease more than 30 years ago,[9,10] inexcitability of the muscle fiber surface membrane was described to be responsible for the hyperkalemic paralysis.[7] Preventive therapy with diuretics such as acetazolamide and thiazides was introduced by McArdle,[16] but this treatment is effective only if the condition is not too severe.

Recent electrophysiological studies on excised intercostal muscle from three such patients[13,15] showed that a high potassium concentration in the bathing solution triggers a noninactivating sodium current through the muscle fiber membranes. This sodium current depolarizes the muscle fibers, rendering them inexcitable. However, many details of the pathomechanism responsible for the weakness are still only poorly understood. The present report provides a more comprehensive evaluation of an additional patient with adynamia episodica, and the results confirm and extend our previous findings.

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CASE HISTORY

The 24-year-old man from Colombia, South America, seemed to be of European and Indian origin. There were a total of 10 family members affected with bouts of periodic paralysis in four generations.[3] His mother, aged 67, still has several attacks of muscle weakness a month. Two brothers and two sisters of the patient are also afflicted, whereas one brother and another sister are not. Neurological investigation was possible in seven afflicted and in two nonafflicted members of the family. All afflicted members showed the same clinical symptoms as our patient.

The patient recalled that his first attack of weakness occurred at age 10. He was unable to walk for half an hour. Subsequently, the attacks increased in frequency. They occurred in the morning almost daily. Usually, the attacks lasted between 30 minutes and 2 hours, but occasionally even longer. Once the patient had to be fed for 3 days because he was so weak.

Between attacks, the patient showed no abnormalities. His muscles were normally developed, with a slight hypertrophy of the calves. No clinical sign of myotonia was detectable, and electromyographic examination of several muscles showed no myotonic runs. During attacks, the lid-lag phenomenon was clearly present, but other myotonic signs, in particular spontaneous activity in the EMG, were absent.

Serum creatine kinase ranged from 150 to 190 U/L (norm < 80 U/L). Histologic evaluation of samples taken from the latissimus dorsi and intercostal muscles revealed a few vacuolated muscle fibers and some nonspecific changes.

METHODS

The study was approved by the Ethics Commission of the Technical University of Munich and was carried out in abidance with the Helsinki convention. The patient gave informed consent to the clinical tests and to the removal of a specimen of his external intercostal muscle.

Clinical Investigations. The studies were usually carried out in the morning before breakfast. To provoke an attack of hyperkalemic weakness the patient was asked to perform work (running up and down stairs or pedalling a bicycle ergometer for 20 minutes). Subsequently he had to lie still for 40 minutes. The serum potassium concentration was determined at short intervals (2–5 minutes).

The force of maximum voluntary isometric contraction of the flexor digitorum muscle and of the quadriceps muscle was recorded. The patient was asked to contract either muscle for 2 seconds and then to relax.[18]

On days in which there were no provoked or spontaneous attacks of hyperkalemic weakness, cold-induced weakness was studied. In the afternoon, the patient had his hand and lower arm submerged for 30 minutes in water of 14–15°C. The force of maximum contraction was measured before cooling, after cooling, and after 1 minute of isometric exercise of the cooled muscle.[18]

In Vitro Experiments. The biopsy of the external intercostal muscle was carried out with general anesthesia (thiopental, fentanyl) and without the use of muscle relaxants. The muscle specimen was dissected into several bundles (500–1000 fibers) which were investigated in different experiments to measure contraction force and excitability,[13] membrane parameters,[19] and the intracellular sodium activity.[1]

The composition of the bathing solution used for transportation, dissection, and experiments has been given elsewhere.[13] All experiments were conducted at 37°C unless otherwise stated. Control values of normal human intercostal muscle that were not available from the literature[12] were determined in fibers from patients who had to undergo thoracic surgery for reasons others than muscle disease. The results are given as mean values ± SD.

RESULTS

Provocation of Hyperkalemic Attacks in the Patient. During exercise serum potassium rose to levels around 5.5 m*M*, as in normal subjects (Fig. 1). After the work it declined to nearly prework levels, but in contrast to the controls, 10 minutes later it rose again to levels around 6.5 m*M*. It was during this secondary rise that the attack of paralysis developed. The elevation of serum potassium usually lasted for an hour or more, then fell spontaneously, often to levels below the initial value. As the serum potassium fell below about 5.5 m*M*, the contraction force slowly recovered. The time course of contractions was not altered during the attacks. For example, the relaxation time of the flexor digitorum muscle was 0.12 msec before and 0.2 msec during an attack, which was considered normal.

The attacks were particularly easy to elicit in this patient. Occasionally the serum potassium was

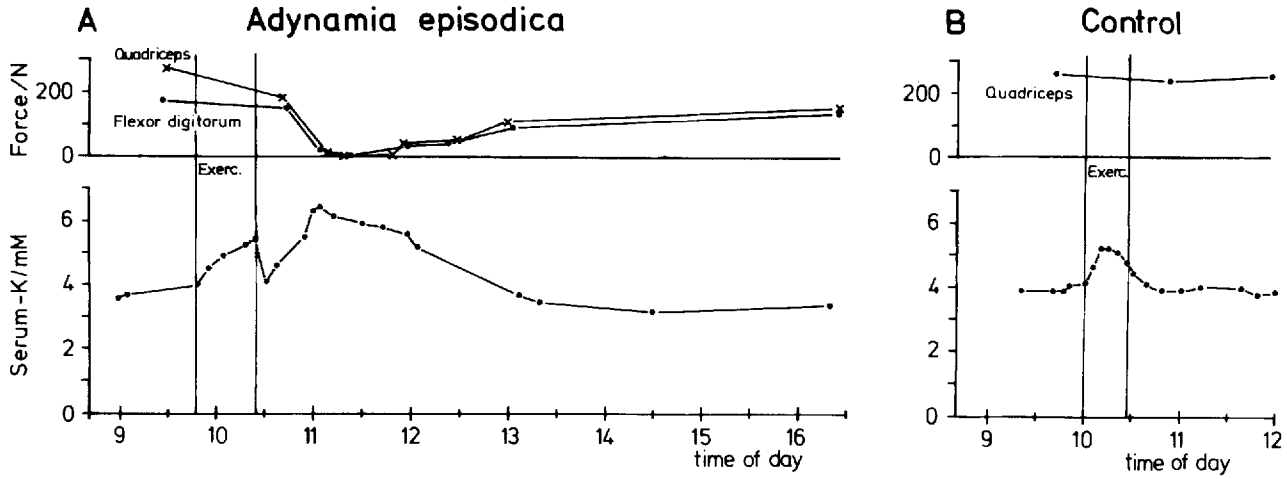

FIGURE 1. Serum potassium and force of the quadriceps and flexor digitorum muscles in the patient and in a control person matched in sex, age, and weight. During an exercise period of about 30 minutes duration, serum potassium rose in patient and control from 4 to 5 m*M*. In the following rest period, serum potassium fell to 4 m*M*. In the patient a secondary rise of the serum potassium occurred up to a level of 6.7 m*M*, and the patient was paralyzed.

higher than the normal range when the patient came into the laboratory in the morning. On these days, after only a few minutes of rest there was an additional rise in serum potassium, and an attack of paralysis occurred (Fig. 2).

Dependence of the Occurrence of Attacks on the Time of Day. During the overnight flight from Colombia to Germany the patient experienced slight muscle weakness in the legs, which he "walked off" in the aircraft. He was examined at 5pm on the day of his arrival. According to his inner clock, this corresponded to 10 am (= 7-hour time difference). At this time, an attack of generalized paralysis developed spontaneously (level of serum potassium 5.3 m*M*). On the second day the patient rested in the morning, but no spontaneous weakness developed (serum potassium 3.0–3.2 m*M*). On the third day at 10 am, the patient performed his first exercise test on the bicycle

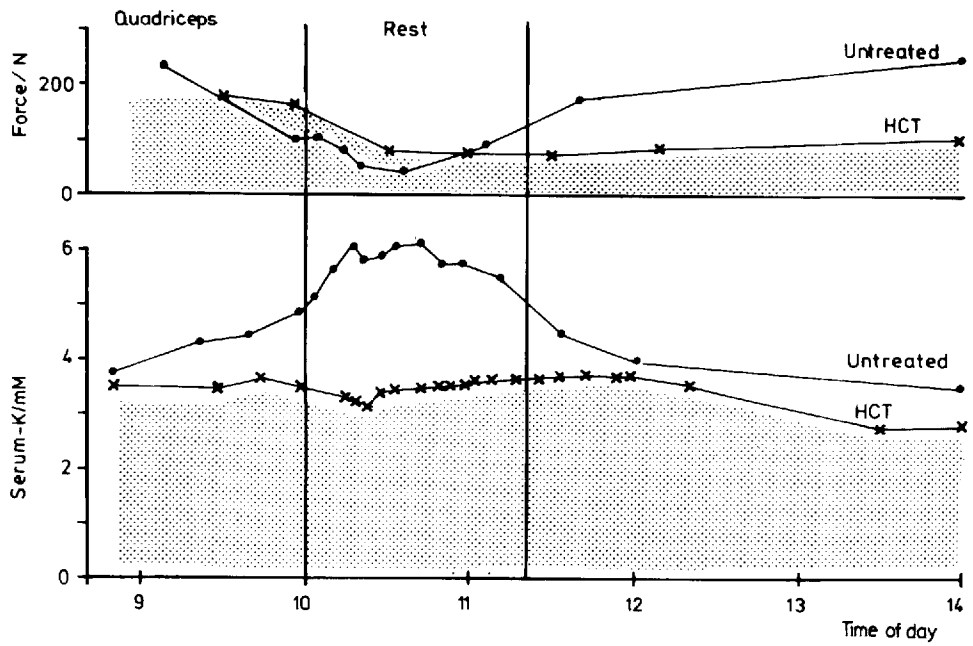

FIGURE 2. Spontaneous attack of paralysis in the morning. Serum potassium rose to 6 m*M*, and the force of the quadriceps muscle was reduced to 1/5 its normal value. Treatment of the patient with hydrochlorothiazide (HCT) resulted in a lower level of serum potassium and prevented the spontaneous rise during rest, but an attack of muscle weakness still occurred.

ergometer. During exercise, the serum potassium rose from 3.5 to 4.8 m*M*, as in normal controls. After the exercise, it immediately fell. No weakness occurred. On the fourth day, the patient had an attack of paralysis in the morning, and for the following 3 weeks attacks were easily provoked in the morning, but never more in the afternoon.

Effect of Drugs. Hydrochlorothiazide (HCT) was given at a dose of 75 mg/day for 5 days. HCT lowered serum potassium and prevented its rise during supine rest in the morning. Even though the serum potassium was lowered by the treatment, definite weakness developed (Fig. 2). A secondary rise in serum potassium to levels of 5 m*M* followed exercise, and severe weakness developed (Fig. 3).

Tocainide was given at a dose of 3 × 400 mg/day for 5 days. As already noted with other adynamia patients,[17] tocainide did not affect the level of the serum potassium or the muscle contraction force during a provoked attack (Fig. 3).

Salbutamol spray was given at the beginning of an attack (0.2 mg) and was repeated after 10 minutes. Muscle force improved, although the level of the serum potassium remained unchanged at 6.3 m*M*. The beneficial effect was short-lasting (Fig. 4).

Local Cooling. When the forearm of the patient was cooled, the EMG of the flexor digitorum muscle did not show spontaneous activity. The force of the flexor digitorum muscle fell to about 10%. The isometric relaxation time increased from 0.12 to 0.3 seconds, which is well within normal limits. The force fully recovered after 45 minutes of rewarming. Serum potassium remained between 4.2 and 4.5 m*M*. A repeat study on another day gave the same results. This protocol was repeated on two other days while the patient was treated with tocainide. The drug did not prevent the local weakness induced by cooling and exercise.

In Vitro Measurements in Intercostal Muscle Fibers at 37°C. The effect of elevating the potassium concentration in the bathing solution on the isometric contraction force was repeatedly tested. The fiber bundles were stimulated with single pulses every 10 seconds. In a typical experiment, an elevation of the external potassium to 6 m*M* produced a decline in twitch force to 23% of baseline within 2 minutes. A further increase in potassium to 7 m*M* caused a decrease to 7%. Normal muscles maintain their twitch force under these conditions. These findings resemble the observations illustrated previously.[13]

Two specimens from the latissimus dorsi were subjected to the contracture test for malignant

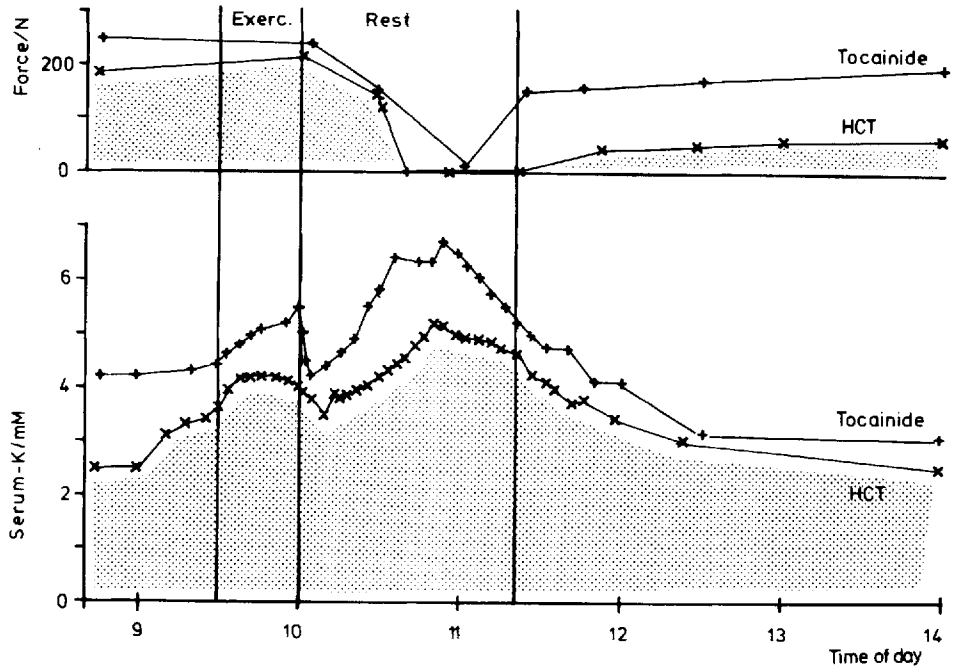

FIGURE 3. Attacks of paralysis provoked by 30 minutes of exercise followed by rest. Patient treated with either HCT or tocainide. Although the serum potassium was lower under HCT treatment, the muscle strength was also diminished throughout the exercise and rest periods. Tocainide did not significantly influence the serum potassium or muscle strength.

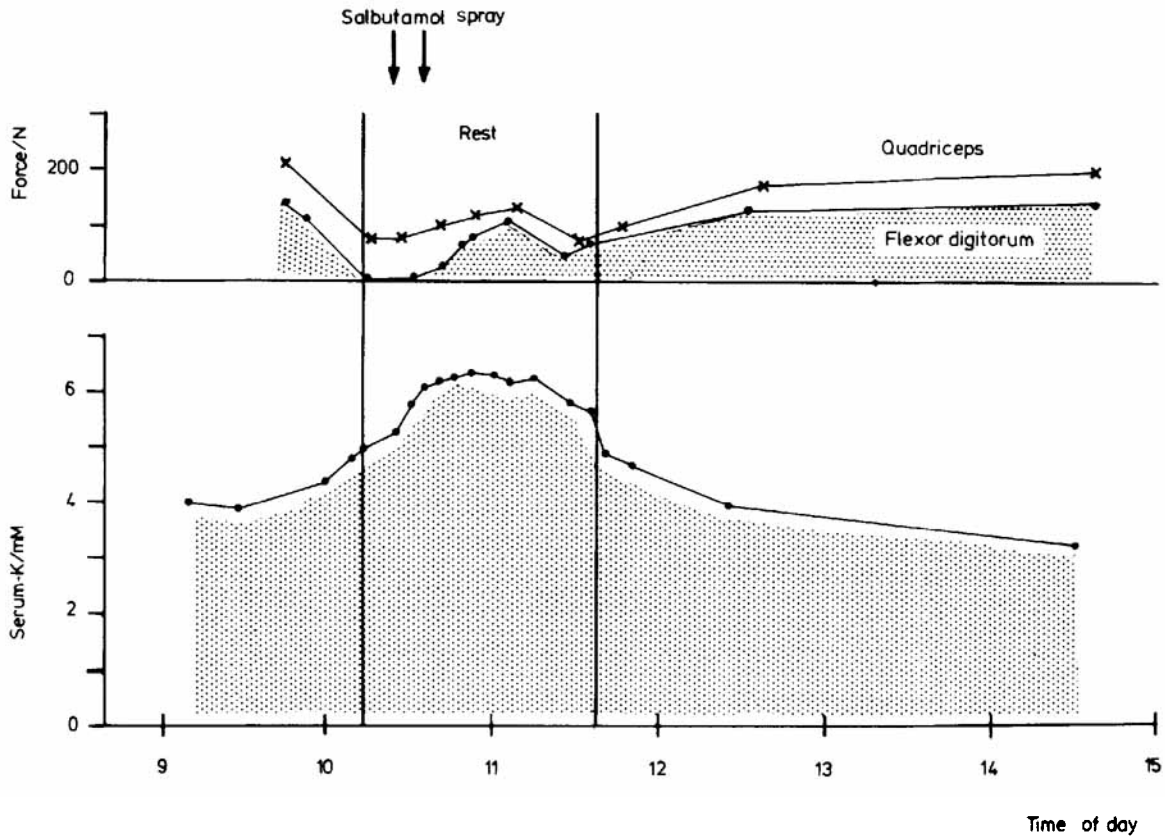

FIGURE 4. The effect of salbutamol on serum potassium and muscle force. An attack of paralysis was provoked by a period of rest in the morning. When the level of the serum potassium had nearly reached 6 m*M* and the force of the finger flexors had fallen to zero, salbutamol was sprayed into the patient's nose in two doses of 0.2 mg. There was no influence of this treatment on the serum potassium, but an improvement of the force was obvious.

hyperthermia.[8] The threshold for caffeine contractures was significantly lower than normal. In both preparations the threshold for contractures was reached at 1.5 m*M*, and contractures >200 mg developed at 2 m*M* caffeine. The normal threshold is at ≥3 m*M* caffeine. However, the response of these fibers to halothane administration (0–4 vol%) was normal.

The resting potential, measured in 10 fibers at 37°C, was −87.6 ± 4.1 mV, i.e., normal. Normal action potentials were elicited in the three muscle fibers tested.

The effects of elevating the extracellular potassium concentration on the resting potential, E_m, were investigated in combination with the application of tetrodotoxin (TTX) or adrenaline (ADR). Typical continuous recordings of E_m are illustrated in Fig. 5. Elevation of the extracellular potassium concentration to 7 m*M* always produced a depolarization that was stronger than predicted by the Nernst equation. This potential change was not reversed when the extracellular potassium concentration was set back to 3.5 m*M*, but TTX was always able to induce repolarization (Fig. 5A). The effects of adrenaline were variable as illustrated in Fig. 5B. In two of six fibers tested it produced a complete repolarization (upper panel), in the other four fibers it only arrested the depolarization process (lower panel).

The intracellular sodium activity at a potassium concentration of 3.5 m*M* of the bathing solution was determined in 11 muscle fibers from 4 normal subjects to 8.5 ± 0.3 m*M*. Compared with this value, the fibers from the patient showed no abnormality. However, when the potassium concentration was raised to 7 m*M*, the intracellular sodium activity increased. This was never observed in control muscles. When TTX was applied, the intracellular sodium activity decreased. This finding indicated that a TTX-sensitive sodium conductance induces the rise of the intracellular sodium activity, because TTX does not block Na^+/H^+ or Na^+/Ca^{2+} exchange systems.

A test of the Na^+/K^+ pump was performed in an experiment in which the activities of both intra-

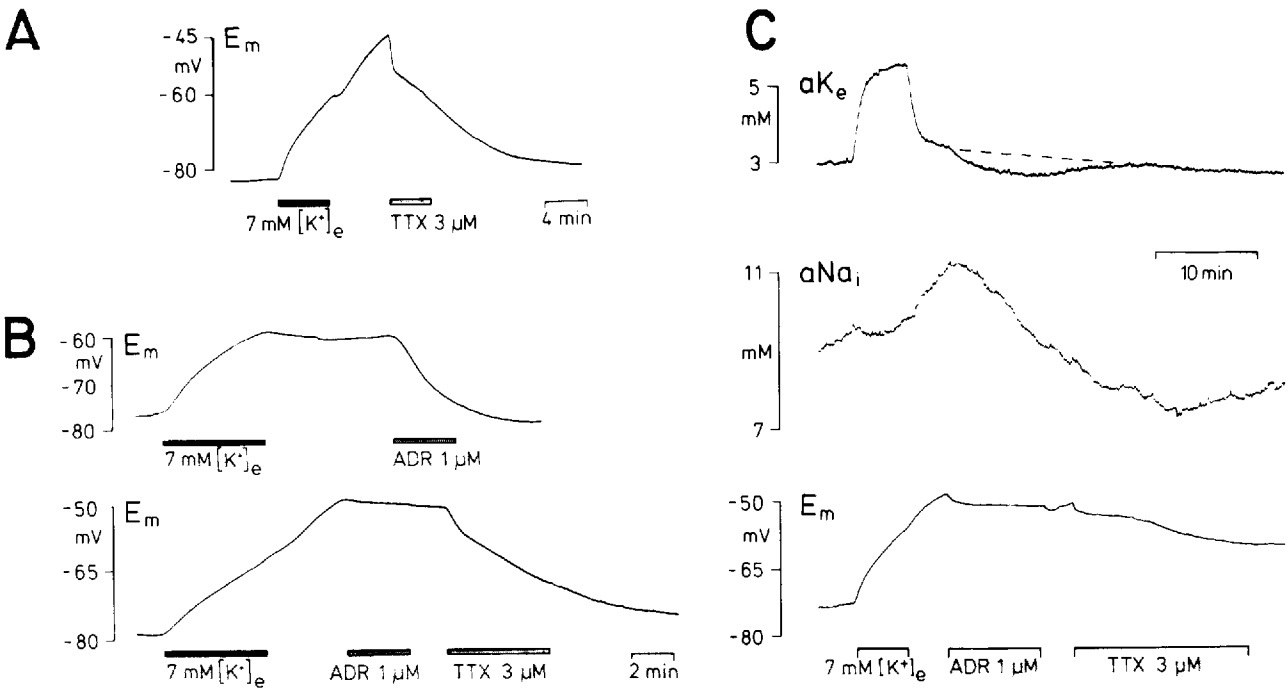

FIGURE 5. Continuous intracellular recordings of the membrane potential, E_m, and of the sodium activity, aNa_i. In each experiment the extracellular potassium concentration of the bathing solution was briefly raised from 3.5 to 7 m*M*, and this caused excessive depolarization. **(A)** Tetrodotoxin (TTX) induced repolarization. **(B)** Adrenalin (ADR) induced repolarization (upper trace) or stopped depolarization (lower trace). **(C)** An additional potassium-sensitive electrode was placed extracellularly within the muscle bundle. During application of 1 µ*M* adrenalin (ADR) the potassium activity in the vicinity of the muscle fibers decreased. For further explanations, see text.

cellular sodium and extracellular potassium were determined while adrenaline was applied (Fig. 5C). This catecholamine is known to stimulate the Na^+/K^+ pump.[5] The potassium-sensitive electrode was placed extracellularly within the muscle bundle and was thus able to record the local deviation of the potassium concentration between the fibers from that in the bathing solution. An excessive fall of the resting potential and an abnormal rise of the intracellular sodium activity was again observed following the increase of external potassium to 7 m*M*. Depolarization of the fiber continued, and the intracellular sodium activity continued to rise after the potassium concentration of the bathing solution was returned to 3.5 m*M*. The addition of adrenaline caused a decrease in the activities of both the extracellular potassium and the intracellular sodium. Despite the fast fall of the intracellular sodium activity, the membrane was repolarized very slowly. The rate of repolarization increased after TTX was added. These results indicate that the abnormal depolarization in this disease is mainly caused by an abnormal conductance rather than by a disturbance of the extra and/or intracellular ion activities.

In Vitro Measurements at Low Temperature. The isometric contraction force of small muscle fiber bundles was measured during brief tetanic stimulation at 4-minute intervals (30 Hz for 300 msec, 0.2 msec pulse duration). Upon a decrease of the temperature from 37 to 27°C, the force declined to 50% within 25 min and to 25% within 50 min. Rewarming the bathing solution to 37°C caused the force to recover to 70% within 2 minutes. In a second preparation, kept at 24°C, there was a full recovery of contraction force following a decrease in extracellular pH to 6.8 (achieved by gassing the bathing solution with a mixture of 40% CO_2 and 60% O_2).

To analyze this cold-induced weakness of the muscle fibers, we measured the electrical membrane parameters at 24°C. No decrease was detected in the resting potential: -83.3 ± 5.8 mV ($n = 18$). The excitability was investigated in 12 fibers. In six of these, action potentials could be elicited with the normal stepwise stimulation. The shape of these action potentials was normal; in particular, the overshoot was ≥20 mV. However, when we looked at these fibers with the dissecting microscope, we could not detect contractions. This is in contrast with our experience with normal fi-

bers. When we slowly increased the temperature while stimulating such a fiber, at 24°C, the fiber did not contract despite a normal action potential; at 26°C a contraction was barely visible; at 28 and 30°C the contraction became more visible; and at 32°C it was strong enough to throw the electrode out of the fiber. The other six fibers studied had a drastically reduced excitability. Three of them did not generate action potentials when the holding potential was −80 mV, and the action potentials elicitable from a holding potential of −90 mV had a slow rise and fall and a peak of −15 mV, i.e., an undershoot. Even with the holding potential increased to −110 mV, none of these 6 fibers produced an action potential with overshoot. None of these abortive action potentials triggered a contraction.

To investigate the cold-induced paralysis further, we estimated the mechanical threshold of the fiber bundles by potassium contractures.[11] In two preparations, the mechanical threshold at 37°C was consistently passed at a potassium concentration of 45 m*M*. In 5 controls the thresholds all were between 40 and 50 m*M*. At 22°C the results from the patient's bundles were less consistent, but in any case the threshold was not passed at potassium concentrations < 100 m*M*. In contrast, the mechanical threshold of control muscles fibers at low temperature remained between 40 and 50 m*M*.

DISCUSSION

The course of an attack of weakness in this patient with severe adynamia episodica without myotonia was very similar as in our previously investigated adynamia patients with myotonia[13] and in a patient with paralysis periodica paramyotonia.[18] When these patients are subjected to an exercise-rest test, the characteristic pattern of the serum potassium level is a normal first rise and fall and an abnormal second rise and fall, during which the weakness develops. A special feature of the present patient was that rest alone was sufficient to produce the weakness.[4]

It is well known that attacks of weakness typically occur in the morning. The influence of the "inner clock" on the susceptibility to attacks of weakness has now been demonstrated by our observations following the 7-hour time shift owing to the patient's long journey. Perhaps the circadian rhythm of the glucocorticoids is involved. The serum levels of glucocorticoids are highest in the morning, and it is known that hyperkalemic attacks of weakness can be induced by administration of these hormones.[21]

Hydrochlorothiazide (HCT) did not prevent the attacks in this severely afflicted patient. HCT therapy maintained a normal serum potassium, but attacks of weakness continued to occur. Muscle force recovered even more slowly than without treatment, perhaps because the Na^+/K^+ pump is less stimulated when the serum potassium is not elevated. When the patient was treated with HCT the attacks were similar as described for normokalemic periodic paralysis. This suggests that the two disorders are very closely related.

Salbutamol, a beta-adrenergic substance, increased the muscle force during an attack, probably by stimulating the Na^+/K^+ pump, as suggested by Clausen et al.[5,22] Metaproterenol, another beta-adrenergic drug, was also reported to enhance the return of muscle strength.[2] The beneficial effect of salbutamol was not mediated via a reduction of the high level of serum potassium.

The in vitro experiments on intercostal muscle fibers confirmed earlier results.[13,15] The resting potential of the muscle fiber surface membrane and the intracellular sodium activity are normal as long as the extracellular potassium concentration is normal. Also the Na^+/K^+ pump of the muscle fiber membrane seems to be normally working. The elevation of potassium in the bathing solution leads to an abnormally large membrane depolarization. The depolarization is caused by an abnormally increased sodium conductance. Elevation of extracellular potassium normally results in a small depolarization of the membrane. In these fibers the small physiological potassium depolarization triggers an abnormal "noninactivating" sodium current. The abnormal sodium current in turn depolarizes the membrane further. This results in inexcitability of the membrane and is the reason for the weakness. In our in vitro experiments an elevation of the extracellular potassium was used to activate the abnormal sodium conductance. It is likely that an increase in serum potassium is also the event triggering an attack in the patients. However, other reasons for membrane depolarization have not been ruled out as triggers for the abnormal sodium current. For example, cell metabolism may decrease the potassium conductance of the membrane by changing the concentration of an intracellular "second messenger."

The abnormal sodium current increases the intracellular sodium. This was demonstrated directly

by the use of Na-selective microelectrodes. Obviously potassium leaves the muscle fibers in compensation, and the extracellular potassium concentration increases. In the patient this vicious circle goes on until potassium excretion by the kidneys and reuptake of potassium by the muscular Na^+/K^+ pumps terminates it.

In the working muscle, physiological liberation of adrenaline and lowering of the intracellular pH antagonize the weakness. In the resting muscle these factors are missing, and under certain not yet understood circumstances the abnormal noninactivating sodium current might even be flowing without being triggered by a work-induced increase of the serum potassium.

Another interesting feature in this patient was the development of local weakness following cooling. This type of weakness has been reported previously.[15] This cold-induced weakness seems to be mediated in a different way than the weakness induced by high extracellular potassium. The muscle fibers did not depolarize in the cold, but they became less excitable and the mechanical threshold increased. Thus the pathomechanism of cold-induced weakness in adynamia episodica hereditaria is different from that in paramyotonia congenita where the muscle fibers depolarize in the cold.[14] Correspondingly the symptoms are different. In paramyotonia, use of the muscles in the cold exacerbates the weakness because every excitation increases the depolarization. In adynamia episodica there is no depolarization, and every excitation improves the weakness. Tocainide prevents cold-induced weakness in paramyotonia because it prevents depolarization; in adynamia episodica it is ineffective. In paramyotonia a rewarmed muscle takes a long time to recover strength because during the long-lasting depolarization the intracellular ion content changes considerably and it takes time to get normal again. In adynamia episodica there is probably no change of the intracellular ion milieau during cooling; therefore, the muscles regain force immediately upon rewarming.

At present we do not know how the existence of an abnormal noninactivating sodium current and the reduced excitability in the cold are related. Abnormal time constants of activation and inactivation of the sodium channels in myoballs cultured from an adynamia episodica patient have been reported.[5,20] The abnormal elevation of the mechanical threshold in the cold and the low threshold of caffeine contractures indicate that the defect may not be limited to just the sodium channels in this disease. There is still no explanation to account for the abnormal rise in serum potassium that develops following a period of rest in these patients.

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