Skeletal muscle fibers from a patient with Schwartz–Jampel syndrome were studied in vitro. The fibers had normal resting membrane potentials, but their resting $[Ca^{2+}]_i$ was elevated. The resting potentials were unstable and spontaneous depolarizations caused twitching in all fibers. Stimulated contractions were characterized by markedly slowed relaxation which was due to electrical after-activity. Neither curare (0.7 μM), tocainide (50 μM), nor phenytoin (80 μM) had an effect on the myotonic activity. In contrast, procainamide (200 μM) suppressed the hyperexcitability without affecting the twitch amplitude. The steady–state current–voltage relation was normal in 5 fibers, but altered in 3 others. These latter fibers had an increased specific membrane resistance owing to a decreased Cl^- conductance. The Na^+ channels were investigated in the cell–attached patch clamp mode. In all patches on either type of fiber, depolarizing pulses elicited delayed, synchronized openings of Na^+ channels. These abnormal openings occurred even after the surface membrane repolarized. We hypothesize that these altered membrane conductances are responsible for the hyperexcitability and the associated slowed relaxation.
Key words: Na^+ channels • patch clamp • 3-electrode voltage clamp • resting myoplasmic $[Ca^{2+}]$ • procainamide • curare • Schwartz–Jampel syndrome

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SCHWARTZ–JAMPEL SYNDROME: II. Na^+ CHANNEL DEFECT CAUSES MYOTONIA

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Schwartz–Jampel syndrome is a rare congenital disorder of muscle and bone with several defined features, such as generalized muscle hypertrophy, multiple skeletal deformities, and spontaneous muscle activity causing extreme muscle stiffness.[1,8,15,28,33] A continuous myotonia is the prominent symptom in all patients.

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Explanations of the pathophysiology underlying this electrical hyperexcitability and stiffness are conflicting. Several authors have contended that curare applied in vivo decreased the extent of the involuntary activity and therefore suggested that the origin may be neural.[5,9,33,34] Others reported that curare had no effect[2,6,22,30] and suggested that the myotonia was due to a defect within the muscle fiber itself. Furthermore, based on single-fiber electromyography, it was suggested that ephapses between muscle fibers are responsible for the myotonia.[15] Possibly the electrical after-activity has different origins in different patients. Nevertheless, most investigators will agree that in this syndrome the hyperexcitability is different from classical myotonia.[2,5,6,9,15,29,33,34]

The present study is the first in vitro investigation to determine the pathophysiology underlying the hyperexcitability and the muscle stiffness in Schwartz–Jampel syndrome. The patient was a 4-year 4-month-old boy whose clinical symptoms were described elsewhere.[30] The parents gave informed consent to a muscle biopsy, which was done before he was started on therapy. Specimens

of the latissimus dorsi and external intercostal muscles were excised under general anesthesia. The investigation was in accordance with the Helsinki convention and was approved by the Ethics Commission of the Technical University of Munich. The operation was completed without complication.

MATERIALS AND METHODS

The specimen of the latissimus dorsi was 3 cm long and had a diameter of about 0.8 cm. The preparation from the intercostal muscle was approximately 1.5 cm long, 1.0 cm wide and 0.4 cm thick. The specimens were kept at 37°C in gassed standard solution (see below) which contained 1 μM tetrodotoxin (TTX, Roth, Karlsruhe, West Germany) to suppress spontaneous activity. Each preparation was dissected into bundles of approximately 2 mm diameter. The bundles were mounted in various experimental chambers for the specific investigations.

Force and EMG. Two bundles of intact fibers from the intercostal muscle were studied. The bundles were stimulated supramaximally with single pulses (0.2 msec duration). Force and EMG were simultaneously recorded as previously described.[14,23] The following agents were added separately to the standard solution: 200 μM procainamide (Sigma, St. Louis, MO, USA); 50 μM tocainide (Astra, Wedel, FRG); 40 and 80 μM phenytoin (Desitin, Hamburg, FRG); and 0.7 μM curare (Alloferin®, Hoffmann-La Roche, Grenzach-Whylen, FRG).

Electrical Membrane Properties. Resting and action potentials were recorded by means of capacity-compensated microelectrodes from both intact intercostal fibers and resealed fiber segments[17] of the latissimus dorsi muscle. Voltage clamp experiments were performed on the same fibers with three microelectrodes.[18] Data collection and analysis were performed by a computer system.[25]

Na^+ Channels. One bundle of the latissimus dorsi muscle was used for patch clamp experiments. The bundle was mounted in a sylgard-bottomed chamber and superfused at 27°C for two hours with a standard solution containing 1–2 mg/mL collagenase (Sigma, type Ia). After this treatment the cell-attached patch clamp technique was employed.[10,12] The data were stored on a modified PCM recorder (Sony, Japan) and evaluated off line. For the compensation of the shunt current, responses without channel activity were averaged and subtracted. Recordings that were stable >10 min were chosen for evaluation.

Myoplasmic $[Ca^{2+}]$. The $[Ca^{2+}]_i$ was determined by means of the fluorescent dye fura-2 in both the intact fibers and the resealed fiber segments. The mean ratio of fluorescence excited at 340 and 380 nm was determined and from this ratio, the mean resting $[Ca^{2+}]$ was estimated.[13] These measurements were made with and without 1.0 μM TTX in the bathing solution. Force was simultaneously monitored throughout.

Solutions. The standard solution used for transportation, dissection, and electrophysiological experiments contained (in m*M*): NaCl 107.7; KCl 3.48; $CaCl_2$ 1.53; $MgSO_4$ 0.69; $NaHCO_3$ 26.2; NaH_2PO_4 1.67; Na gluconate 9.64; glucose 5.5; sucrose 7.6 (315 mosm/L). The Cl^- free solution used in some of the voltage clamp experiments was made by 1) replacing NaCl and KCl with the respective methane sulfonate salts, 2) replacing $CaCl_2$ with Ca gluconate, and 3) omitting the sugars 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% O_2 and 5% CO_2.

Statistical differences were determined by Scheffe's multiple contrast (nonparametric) test.

RESULTS

EMG and Force. When TTX was removed from the bathing solution, all preparations developed spontaneous electrical activity and force. On stimulation with a single pulse, the fibers contracted and the relaxation was markedly slowed. The electrical activity was enhanced during this slowed relaxation phase (Fig. 1). Repetitive stimulation at 0.5 to 1.0 Hz neither decreased nor further increased the myotonic activity (i.e., lack of "warm-up phenomenon"). Mechanical perturbation such as a transient removal of the bathing solution caused spontaneous electrical activity and sustained force.

We observed no change in the spontaneous activity upon the addition of (1) curare (0.7 μM tubocurarine); (2) tocainide (50 μM) (Fig. 2) or (3) phenytoin (40 and 80 μM). TTX (1 μM) reversibly rendered the muscle electrically and mechanically silent (Fig. 2). Procainamide (200 μM) was the only therapeutically usable drug which had an effect on both the spontaneous activity and the af-

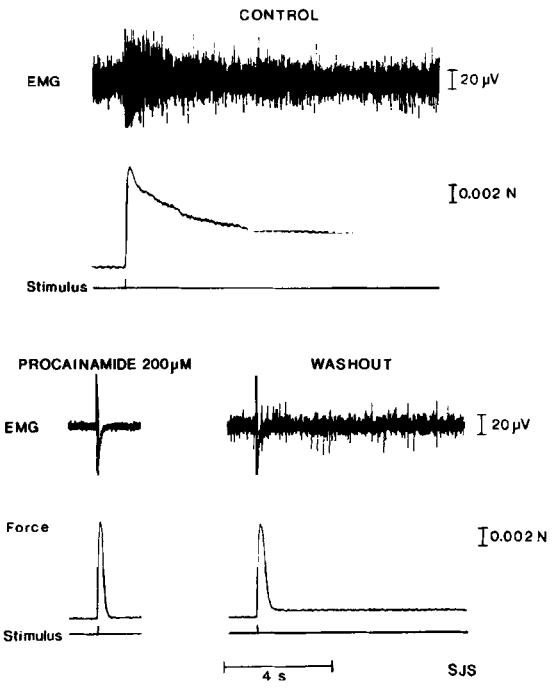

FIGURE 1. Long-lasting electrical after-activity and slowed relaxation recorded in vitro. Upper panel: before the application of procainamide. Note the large amount of spontaneous activity even prior to stimulation. Lower panel: procainamide (200 μM) greatly reduced spontaneous basal activity and after-activity, but did not decrease the size of the twitch.

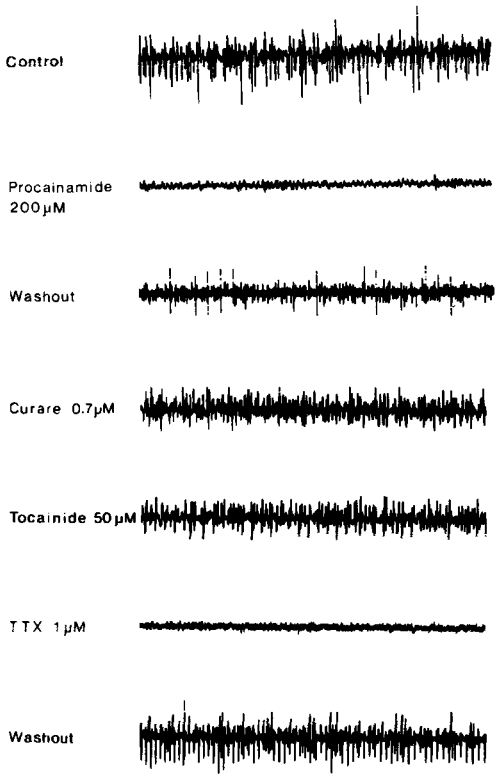

FIGURE 2. The effects of various drugs on the spontaneous electrical activity. Procainamide (200 μM) and tetrodotoxin (TTX) (1 μM) were effective in reversibly blocking this spontaneous electrical activity. In contrast, curare (0.7 μM) and tocainide (50 μM) had little or no effect.

ter-activity (Figs. 1 and 2). In the presence of procainamide, the twitch amplitude was slightly increased. The dense spontaneous activity, which was present prior to the exposure to the drug, had probably caused many fibers to be in a fatigued state. The therapeutic effects of procainamide were reversed following washout (Figs. 1 and 2).

Resting and Action Potentials. The mean resting membrane potentials did not differ between the resealed fiber segments and the intact fibers ($P > 0.2$); the respective values were -83.2 ± 9.0 mV ($\bar{x} \pm$ SD; n = 13) and -85.3 ± 5.6 mV (n = 28). TTX (1 μM) had no effect on the resting potential.

In contrast to normal muscle, the intact fibers and the fiber segments from our patient showed repetitive activity which occurred spontaneously or was induced within seconds by impaling a fiber with a microelectrode (Fig. 3). Spontaneous activity occurred not only in "high resistance fibers" (see section on Current-Voltage Relationships), but also in fibers with normal membrane resistance (i.e., normal CL^- conductance). The repetitive activity lasted up to several minutes. The bursts were usually terminated when the fiber membrane became depolarized to values between -50 and -40 mV. Quite often fibers repolarized spontaneously and subsequently myotonic activity restarted (Fig. 3C).

As expected, the amplitude of an action potential within a run became smaller when the membrane depolarized. During this slow depolarization, the action potentials frequently split up into two peaks (Fig. 3). The duration between the two peaks changed in a regular manner. In addition to the splitting up of action potentials, often additional regularly occurring potentials were recorded. For example, as shown in the last trace of Fig. 3A, a third recurring potential was observed, which had a slower frequency than the potential that had split up (i.e., it occurred out of phase with the split potential). Hence, in some fibers multiple sites of locally gated currents were identified. Furthermore, it appears that these potential changes did not necessarily propagate along the whole length of a fiber (i.e., the recorded potentials of these depolarized fibers were due to local

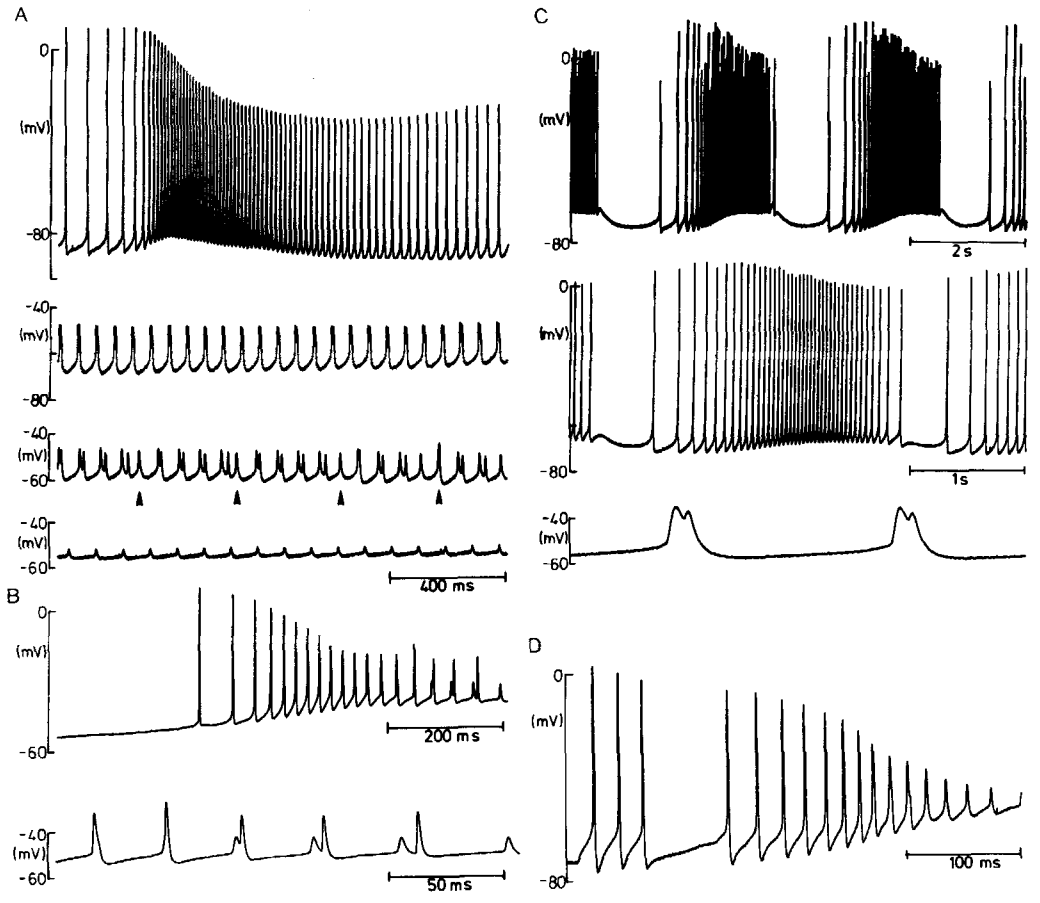

FIGURE 3. Spontaneous long-lasting runs of action potentials recorded intracellularly. (A) Four traces from a spontaneous run which lasted about 1 min (intercostal fiber); note doublets of action potentials in the second and third trace. (B) Short run with doublets; note in the lower trace that the amplitude of the second spike was larger (intercostal fiber). (C) Bizarre rhythmic activity; eventually the frequency of the spontaneous activity stabilized, but subsequently doublets occurred (intercostal fiber). (D) Spontaneous run of action potentials (resealed fiber segment, latissimus dorsi muscle).

currents). In summary, "complex repetitive discharges" were observed at the single-fiber level.

Current–Voltage Relationships. For five out of eight fibers the steady-state current-voltage relationships were very similar to those of normal fibers (Fig. 4). Nevertheless, in all fibers (in TTX-free solution) repetitive activity was recorded intracellularly. In the remaining three fibers, the current–voltage relationship had a low slope at the "zero current" potential, reflecting a low membrane conductance, g_m (Table 1). The mean conductance value of these latter three fibers was 86 $\mu S/cm^2$, compared to 205 $\mu S/cm^2$ for the other five and 175 $\mu S/cm^2$ for fibers from normal subjects.[16] For the determination of the component conductances, the current–voltage relationships were recorded in a Cl^- free solution containing TTX (Fig. 4). In this solution the slope of this relationship reflects the K^+ conductance, g_k; it was normal in all fibers (Table 1). The difference between the relationships measured in the presence and absence of Cl^- represents the Cl^- conductance and its dependence on the membrane potential. Hence, the slope of this curve at the "zero current" potential represents the resting Cl^- conductance of the membrane, g_{Cl}. This value was significantly lower ($P < 0.01$) for the "high resistance" fibers than for the "normal resistance" fibers of this patient, and for fibers from normal controls.[16]

Na^+ Channels. After a bundle was treated with collagenase, it was fairly easy to obtain giga-ohm seals using the cell-attached mode. Inside-out patches were more difficult to obtain because of their instability. Therefore, we report only data recorded in the cell-attached mode. The patches

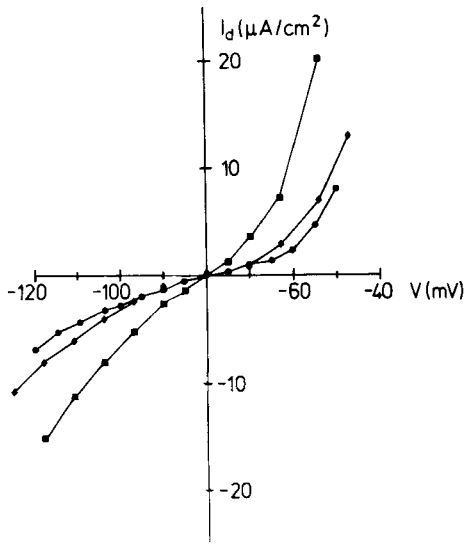

FIGURE 4. Current–voltage relationships in standard solution of normal (■, n = 5) and high (◆, n = 3) resistance fibers from a patient with SJS. In addition, current–voltage relationships were determined in Cl^- free solution (●, n = 3). For all fibers, the holding potential equaled the resting membrane potential which was approximately −80 mV. Data from both intact fibers and fiber segments were included.

were stable for up to 20 minutes. In total, data were obtained from nine fibers.

The holding potential was the sum of the resting potential determined later in the whole cell recording mode and the patch potential. The Na^+ channels within a patch were activated by depolarizing voltage steps.

Table 1. Membrane parameters of muscle fibers obtained from a patient with Schwartz–Jampel syndrome.

	Normal resistance fibers	High resistance fibers
R_m (Ω cm²)		
1	3228	10,632
2	4237	11,427
3	5890	12,882
4	5898	—
5	7012	—
	5253 ± 1504	11,647 ± 1141
g_m (μS/cm²)	205 ± 67 (n = 5)	86 ± 9 (n = 3)
g_{Cl} (μS/cm²)	130 ± 71 (n = 5)	12 ± 24 (n = 3)
g_K (μS/cm²)	74 ± 24 (n = 3)	
E_m (mV)	−84.6 ± 4 (n = 41)	

Note: Determinations at 37°C. Specific membrane resistance, R_m; membrane conductance, g_m; component conductances for chloride (g_{Cl}) and potassium (g_K), which was determined in Cl^- free solution. Numbers of fibers in brackets. Averaged data are represented as $\bar{X}$ ± SD.

Fig. 5A shows openings of Na^+ channels in the membrane of a control muscle stimulated with two different depolarization steps. Several Na^+ channels were activated simultaneously immediately after the beginning of the depolarizing pulse, and with a certain delay they were inactivated. Reopenings were not observed. This behavior of Na^+ channels was regularly observed in control patches.[10,11]

Fig. 5B shows activations of Na^+ channels in a patch of a muscle fiber of our patient. In contrast to controls, the Na^+ channels were often activated with a delay (Fig. 6). This delay was variable, yet often the openings of the Na^+ channels were synchronized. In addition, gating of the Na^+ channels was observed even after repolarization of the membrane patch (see second trace of the left part of Fig. 5B). On the other hand, as in normal patches the Na^+ channels were inactivated within a few milliseconds in a potential–dependent manner.

In Figure 6, a "macroscopic" Na^+ current (I_{Na}) was reconstructed by averaging 70 activations, like those shown in Fig. 5. The variable latency between beginning of depolarization and synchronized channel activations slowed the onset of I_{Na} and led to a longer decay time. The time constant of decay of the "macroscopic" I_{Na}, however, does not correspond with the time constant of inactivation of the channels. The microscopic inactivation of the average current through single Na^+ channels was on the average normal and it was the delayed synchronized openings of Na^+ channels that resulted in an increase of the current duration (Fig. 5).

Myoplasmic $[Ca^{2+}]$. The mean fluorescence ratios determined for the fibers in two intercostal bundles was 0.070 ± 0.013 ($\bar{X}$ ± SD; n = 40) in the presence of TTX. According to our calibration,[13] this ratio corresponds to an $[Ca^{2+}]_i$ of 0.22 μM. This value was significantly ($P < 0.01$) higher than in normal muscle preparations: 0.10 μM (n = 208).[17] TTX was washed out (15 min) in one preparation without a significant change in the $[Ca^{2+}]_i$. The mean 340/380 fluorescence ratio in the resealed fiber segments of the latissimus dorsi was not different from the intact intercostal fibers: 0.076 ± 0.16 (n = 12) which corresponds to a $[Ca^{2+}]_i$ of 0.30 μM. Fura-2 had no effect on the resting membrane potential of the muscle fiber. At the end of the fluorescence experiments the mean resting potential was −81.5 mV (n = 12).

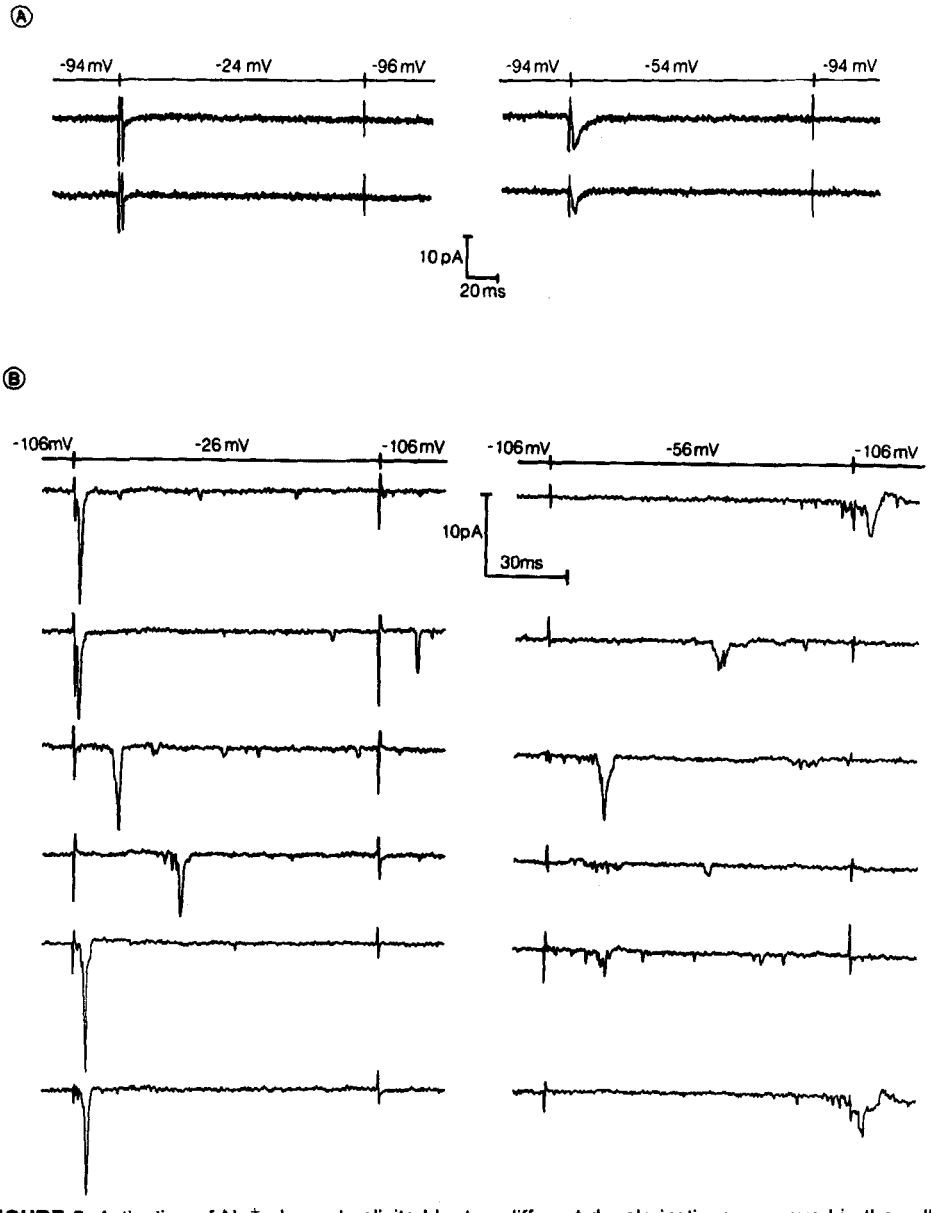

FIGURE 5. Activation of Na^+ channels elicited by two different depolarizations measured in the cell-attached mode. **(A)** Patches from a resealed fiber segment of a normal muscle (vastus medialis). **(B)** Currents recorded from resealed fiber segment obtained from the Schwartz–Jampel patient (latissimus dorsi). The shunt current was compensated (see Methods). The records were low-pass filtered at 2 kHz. Openings of Na^+ channels in (B) appeared even after repolarization of the membrane patch.

DISCUSSION

The spontaneous activity and the twitch after-activity seen in our preparation did not disappear when curare was applied in high concentrations. Therefore, the electrical activity in this case was myogenic and not neurogenic. This result and also the findings of others[2,6,22,30] are in contrast with several studies contending an effect of curare on spontaneous activity.[5,9,33,34] It appears that this activity has different origins in different patients.

The pattern of this electrical activity was not the same as that described for myotonia congenita or recessive generalized myotonia.[14,21,26,31] These "classical" myotonias are characterized both in vivo and in vitro by short-lasting bursts with modulation of frequency and amplitude of action potentials.[14,26] The electrical activity recorded from this Schwartz–Jampel patient resembled more the activity recorded from patients with myotonic dystrophy.[11]

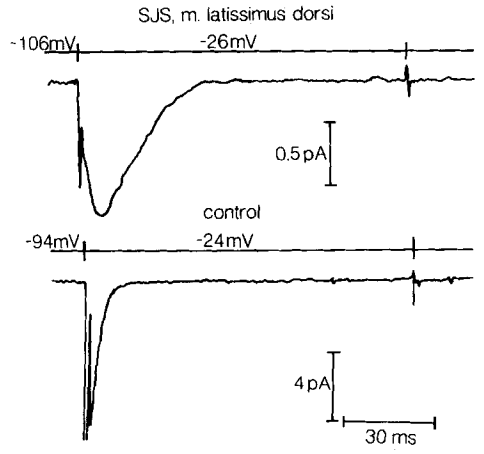

FIGURE 6. Averages of 70 activations of Na^+ channels from a normal muscle (below) and from a resealed fiber segment obtained from the Schwartz–Jampel patient (above). Different scales of ordinates were used for better comparison of time constants of onset and decay.

Procainamide, which blocks Na^+ channels in an open state,[32] abolished this activity. In contrast, tocainide had little effect. For patients with recessive generalized myotonia, myotonia congenita or paramyotonia this agent is quite effective.[18,23,24,26,31] Tocainide blocks Na^+ channels in an inactivated state.[32] This may imply that the defect in the Na^+ channel in Schwartz–Jampel syndrome is different than in other myotonias.[4,11] Likewise, in this Schwartz–Jampel patient, the so-called "warm-up" phenomenon that is a characteristic feature of myotonia congenita and recessive generalized myotonia was minimal or lacking.[30] Hence, we conclude that the cause of myotonic activity in this Schwartz–Jampel patient was different from the membrane defect found in these other two diseases.[26]

Two membrane defects could explain this abnormal activity: First, in several fibers the Cl^- conductance was reduced, as described for other myotonic disorders: myotonia congenita of goats[3] and humans[20]; myotonic dystrophy[21]; and recessive generalized myotonia.[26] Second, we observed an abnormal behavior of the Na^+ channels which we had never observed in patches of normal muscle.[10] The number of these synchronized late openings was so large that the shape of the averaged Na^+ current was altered. This was different from what we observed for the Na^+ channel in muscle from patients with myotonic dystrophy, in which late openings of the Na^+ channel were always preceded by an early activation of Na^+ channels.[11] Synchronized late openings of the Na^+ channels were a characteristic of all fibers investigated here. They may account for the occurrence of split action potentials and for the multiple sites from which local currents produced spike potentials of varying frequencies. These multifocal sites of synchronized openings producing local currents did not occur until the membrane was depolarized and thus incapable of propagating action potentials. The synchronized late openings could be the result of a structural defect of the Na^+ channel itself, an alteration in the surrounding lipid membrane, or an altered intracellular control of Na^+ channel gating. We found, however, that in several diseases Na^+ channel alteration is associated with a reduced Cl^- conductance. As in these hereditary diseases only one gene is affected, a defect of the channel protein itself is not very probable.[27]

In all muscle bundles we studied from this patient, the resting intracellular $[Ca^{2+}]$ was elevated relative to controls.[17] This elevation in myoplasmic $[Ca^{2+}]$ did not appear to be produced by excessive spontaneous electrical activity, because the concentration remained elevated in the presence of TTX. It is likely to be correlated with the changes in morphology reported by Spaans et al.[30] They noted an interruption in the sarcomeres including the Z disks, increased incidence of vacuoles and a focal disarray of the myofibrils. Furthermore, it has been reported that an elevation of myoplasmic $[Ca^{2+}]$ is associated with the activation of proteases[7,19] which may have induced the observed morphological changes.

We conclude that the skeletal muscle from this patient with Schwartz–Jampel syndrome was affected by several different defects which included an abnormal Na^+ channel gating, reduced Cl^- conductance (in one fiber population) and an altered regulation of myoplasmic free Ca^{2+}. Procainamide, by blocking the synchronized openings of Na^+ channels, may aid in reducing some of the symptoms in this patient, which are related to continuous muscle activity.

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