Loss of Electrical Excitability in an Animal Model of Acute Quadriplegic Myopathy

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In rats treated with high-dose corticosteroids, skeletal muscle that is denervated in vivo (steroid-denervated [S-D]) develops electrical inexcitability similar to that seen in patients with acute quadriplegic myopathy. In studies of affected muscles in vitro, the majority of S-D fibers failed to generate action potentials in response to intracellular stimulation although the average resting potential of these fibers was no different from that of control denervated muscle. The downregulation of membrane chloride conductance ($G_{Cl}$) seen in normal muscle after denervation did not occur in S-D muscle. Although block of chloride channels in S-D muscle produced high specific membrane resistance, comparable to similarly treated control denervated muscle, and partially restored excitability in many fibers, action potential amplitude was still reduced in S-D fibers, suggesting a concomitant reduction in sodium current. $[^3]$H-saxitoxin binding measurements revealed a reduction in the density of the adult muscle sodium channel isoform in S-D muscle, suggesting that a decrease in the number of sodium channels present may play a role in the reduction of sodium current, although altered properties of channels may also contribute. The weakness seen in S-D muscle may involve the interaction of a number of factors that modify membrane excitability, including membrane depolarization, persistence of $G_{Cl}$, and reduced voltage-gated sodium currents.


Acute quadriplegic myopathy (AQM) was first described by MacFarlane and Rosenthal in 1977 in a patient with asthma who was treated with corticosteroids and neuromuscular blocking agents. It has subsequently been recognized that an acute myopathy appearing in the setting of critical illness is a relatively common entity.2–4 The classic clinical picture is that of an asthmatic patient intubated for an exacerbation, treated with corticosteroids and neuromuscular blocking agents, who subsequently develops an acute quadripareisis.5,3–11 Nerve conduction studies reveal diminished compound muscle action potential amplitudes in the setting of normal sensory nerve action potential amplitudes, with myopathic motor units and scattered spontaneous activity on electromyography.3,4,12–17 The etiology of the rapid and dramatic weakness in this disorder is poorly understood.

It has been demonstrated that affected skeletal muscle in AQM is inexcitable to direct electrical stimulation.16,17 To determine the factors that lead to loss of muscle electrical excitability in this disease, it would be useful to establish an animal model. Treatment of denervated rat muscle with corticosteroids results in weakness that is accompanied by changes of muscle cytoarchitecture similar to those seen in patients with AQM,3,4,18–22 raising the possibility that concurrent denervation and steroid treatment in rats in vivo might provide such a model.

We performed intracellular recording from steroid-treated, denervated (S-D) rat muscle fibers and established that there is loss of electrical excitability. We examined passive membrane properties of inexitable S-D muscle fibers as well as the characteristics of action potentials from S-D muscle that were excitable. Our data suggest that several factors reduce membrane excitability in S-D muscle, including denervation-induced membrane depolarization, steroid-induced persistence of membrane chloride conductance ($G_{Cl}$) after denervation, and reduction of sodium conductance in S-D muscle.

Materials and Methods

Denervation and Corticosteroid Treatment

Adult (200–400 g body weight) male and nonpregnant female Sprague-Dawley rats were denervated by removing a 10-mm segment of the left sciatic nerve in the upper thigh.

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under intraperitoneal (IP) anesthesia (350 mg/kg chloral hydrate). Dexamethasone (5 mg/kg) was injected subcutaneously in the paraspinal region beginning the day of denervation and continuing daily for 8 to 10 days. Rats were sacrificed by carbon dioxide inhalation.

**Light Microscopy and Immunocytochemistry**

For histochemical studies, 10-μm cryostat sections of extensor hallucis longus were processed for either hematoyxin-eosin or adenosine triphosphatase (ATPase) (preincubation pH 9.4) staining. For immunocytochemistry, cryostat sections were incubated with mouse monoclonal antibody directed against type 2A myosin heavy chain (kindly provided by Stefano Schiaffino) for 1 hour, rinsed, and then incubated with a fluorescein-tagged goat anti-mouse antibody (Jackson ImmunoResearch Laboratories, West Grove, PA).

**Electrophysiology**

For measurement of the compound muscle action potential (CMAP) from the tibialis anterior muscle in vivo, rats were anesthetized with chloral hydrate (350 mg/kg IP) 8 to 10 days after denervation. Muscle was directly stimulated, as has previously been described. Where indicated, chloride channels were blocked with anthracene-9-carboxylic acid (9-AC; 25 μM). The values of specific membrane resistance in this report are higher than those previously reported by our laboratory and others. High-resistance microelectrodes (15–60 MΩ) and small depolarizations were used in this study owing to the mechanical instability of S-D fibers. To determine whether this contributed to the higher estimate of specific membrane resistance obtained, we directly compared high- and low-resistance electrodes in control muscle. Using low resistance (5 MΩ) electrodes, we obtained an estimate of specific membrane resistance of 600 Ω cm², comparable to our own previously published values, suggesting that use of high-resistance electrodes and small test pulses contribute to the higher estimates of specific membrane resistance reported here. This may be due to sampling of a smaller region around the electrode, with concomitantly less contribution from T-tubular elements. However, this issue does not affect the conclusions in our study because all of the measurements reported here were made in an internally consistent manner.

Action potentials were elicited using 5- to 15-msec depolarizing pulses. Currents of up to 100 nA were used that resulted in depolarizations of 40 to 70 mV. Voltage threshold of the regenerative response was defined as the point of inflection of the first derivative of the action potential trace. A fiber was considered inexcitable if either (1) a depolarizing pulse to a potential of greater than −30 mV resulted in no identifiable threshold or (2) contraction of the impaled fiber occurred before detection of a threshold.

**Measurement of Intracellular Sodium**

Muscle was weighed and homogenized in a 5-fold quantity of water (weight per weight). The homogenate was spun for 10 minutes at 6,000 rpm, and the supernatant was concentrated 10-fold using a Speedvac (Savant). Sodium and potassium were measured using a Johnson and Johnson Vitros 950 with ion-selective electrodes.

**3H-Saxitoxin Binding Assays**

Sarcosome was isolated and 3H-saxitoxin (STX) binding was performed as previously described. Membrane protein and cholesterol were measured using standard chemical assays.

**Statistical Analysis**

Data from multiple treatment groups was analyzed using a nested analysis of variance. Comparisons between individual groups were done using Student’s t test.

**Results**

**Muscle Electrical Excitability**

To determine whether treatment of denervated rat muscle with corticosteroids alters electrical excitability, we evaluated the response of tibialis anterior (TA) muscle in vivo to direct electrical stimulation using the same technique described previously to stimulate muscle in patients with AQM. Compound muscle action potential amplitudes (CMAPs) were averaged from five TA muscles, using control muscle, denervated muscle, innervated steroid-treated muscle, and S-D muscle. Although the CMAP of control-denervated muscle did not differ significantly from control or innervated steroid-treated muscle (p < 0.20), the mean CMAP amplitude of S-D muscle was significantly smaller (p = 0.01; Table 1). Although the number of rats examined was small, the decrease in CMAP in S-D muscle suggested that treatment of denervated rat muscle with corticosteroids might lead to a loss of muscle electrical excitability in some muscle fibers that is similar to that seen in patients with
AQM. To examine this possibility further we performed intracellular recording (see later).

**Muscle Pathology**

On hematoxylin-eosin staining there was evidence of dramatic atrophy of fibers in S-D muscle (Fig 1). The loss of ATPase and myosin immunostaining shown in Figure 1 is similar to that previously reported in the animal model of AQM. Previous studies have demonstrated that in the rat model there is a loss of thick filament similar to that seen in patients with AQM.

**Intracellular Measurements**

Resting membrane potentials (RMPs) and membrane excitability were assessed by intracellular recordings in EDL muscle from each test group after acute transfer to a recording chamber. In control EDL, depolarizing current pulses easily elicited action potentials in 100% of impaled fibers. Steroid treatment alone or denervation in the absence of steroids did not significantly affect excitability (action potentials in 96% of fibers after either treatment). However, in S-D EDL, many fibers could not be stimulated to fire action potentials despite depolarizing currents of up to 100 nA, whereas other fibers produced action potentials of abnormally low amplitude. S-D muscles were not equally affected. In 15 of the 20 S-D muscles studied, the majority of fibers were inexcitable, with only 16 of 93 impaled fibers (17%) producing action potentials in response to depolarization. In the remaining 5 muscles, most fibers (80%) were still able to generate action potentials.

To assess the contribution of depolarization of the RMP to the loss of excitability, we analyzed the RMP in the 15 most affected S-D muscles and compared these results to control, steroid treated, and denervated muscle (see Table 1). In control muscle, the mean resting potential was $-81.7 \pm 1.5$ mV. Steroid treatment of innervated muscle did not alter the resting potential ($78.7 \pm 1.0$). The mean resting potential in control denervated fibers decreased to $-60.7 \pm 1.0$ mV, consistent with the known effects of denervation on skeletal muscle. In S-D fibers from the most severely affected EDLs, the RMP was $-59.5 \pm 0.7$ mV, indistinguishable from control denervated fibers.

We also analyzed data within the S-D group to determine whether there was a significant difference in RMP between inexcitable and excitable fibers in the 15 severely affected S-D muscles. The mean resting potential of fibers lacking an action potential was $-59.9 \pm 0.6$ mV ($n = 77$) versus $-63.3 \pm 1.5$ mV ($n = 16$) for fibers with action potentials ($p = 0.08$). Although fibers with more negative resting potentials were more likely to be excitable, there was extensive overlap in resting potentials between excitable and inexcitable fibers. Eleven fibers from S-D muscles that had resting potentials of $-70$ mV or greater lacked action potentials.

**Contraction of Inexcitable Fibers**

Real-time video images of some fibers from affected S-D muscles were monitored during intracellular current injection. Despite the absence of an action potential and the presence of dantrolene, local activation of contractile elements was clearly evident with large depolarizing current pulses that produced local fiber depolarization to between $-30$ and $-10$ mV. This was sufficient to activate excitation-contraction coupling in the absence of an endogenous action potential, suggesting that the mechanisms for excitation contraction coupling are at least partially intact in electrically inexcitable fibers.

**Passive Membrane Properties of Inexcitable Fibers**

Because alterations in passive membrane properties might contribute to the lower excitability of S-D fibers, we measured these properties in single muscle fibers from each treatment group. In control EDL we obtained a specific membrane resistance of $2,140 \pm 482$ $\Omega$ cm$^2$ and a time constant of $4.02 \pm 0.40$ msec.

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**Table 1. Muscle Excitability and Passive Membrane Properties**

<table>
<thead>
<tr>
<th></th>
<th>Control Innervated</th>
<th>Control Denervated</th>
<th>Steroid Innervated</th>
<th>Steroid Denervated</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMAP amplitude (mV)</td>
<td>14.6 ± 4.3 (n = 5)</td>
<td>8.8 ± 1.6 (n = 5)</td>
<td>9.2 ± 0.9</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>Fibers with AP</td>
<td>80/80</td>
<td>121/126</td>
<td>75/78</td>
<td>16/93</td>
</tr>
<tr>
<td>Resting potential (mV)</td>
<td>$-81.7 \pm 1.5$</td>
<td>$-60.7 \pm 1.0$</td>
<td>$-78.7 \pm 1.3$</td>
<td>$-59.5 \pm 0.7$</td>
</tr>
<tr>
<td>Input resistance (MΩ)</td>
<td>0.41 ± 0.03</td>
<td>0.73 ± 0.11</td>
<td>0.34 ± 0.03</td>
<td>0.75 ± 0.03</td>
</tr>
<tr>
<td>Radius (µm) of recorded fibers</td>
<td>30.9 ± 3.8</td>
<td>25.0 ± 2.6</td>
<td>31.5 ± 1.9</td>
<td>19.4 ± 1.9</td>
</tr>
<tr>
<td>Membrane resistance (Ω cm$^2$)</td>
<td>2,140 ± 482</td>
<td>3,402 ± 830</td>
<td>1,478 ± 77</td>
<td>1,745 ± 538</td>
</tr>
<tr>
<td>Time constant (msec)</td>
<td>4.02 ± 0.40</td>
<td>6.02 ± 0.65</td>
<td>3.56 ± 0.24</td>
<td>4.70 ± 0.34</td>
</tr>
</tbody>
</table>

*Electrical excitability and passive membrane properties of skeletal muscle after denervation, steroid treatment, or both. All data are shown as mean ± SEM. Mean compound muscle action potential (CMAP) was recorded in vivo. All other data in the table are from in vitro intracellular recording (see Materials and Methods). At least 8 fibers were studied for each rat. n = number of rats studied; AP = action potential.*
which increased to $3,402 \pm 830 \, \Omega \, \text{cm}^2$ and $6.02 \pm 0.65 \, \text{msec}$ 8 to 9 days after denervation (see Table 1). This increase in specific membrane resistance and time constant reflects the known decrease in membrane chloride conductance that follows denervation.\textsuperscript{28,31} After steroid treatment, the specific membrane resistance and time constant in innervated fibers were $1,478 \pm 77 \, \Omega \, \text{cm}^2$ and $3.56 \pm 0.24 \, \text{msec}$. Denervation in the presence of steroid did not produce the expected rise in membrane resistance ($S-D = 1,745 \pm 538 \, \Omega \, \text{cm}^2$).
and resulted in only a small increase in time constant compared with control (4.70 ± 0.34 ms), which was not statistically significant.

Control and steroid-treated denervated fibers were exposed in vitro to 9-AC, a specific inhibitor of skeletal muscle chloride channels, at a concentration (25 μM) known to block over 80% of muscle chloride conductance.27 Because approximately 85% of the resting membrane conductance is GCl in normal rat skeletal muscle,9-AC produces a marked increase of specific membrane resistance in normal muscle.27 Exposure of S-D fibers to 9-AC also produced a dramatic increase in specific membrane resistance, resulting in a final value similar to that found in 9-AC-treated denervated control muscle. These results confirm that the lack of increase in membrane resistance in S-D fibers is secondary to persistent expression of chloride channels after denervation (Table 2).

We then examined the effect of blocking GCl on the excitability of 4 severely affected S-D muscles. In these muscles, none of 19 fibers were able to generate an action potential before treatment with 9-AC. More than half (22/39) regained some regenerative response after exposure to this chloride channel blocker. However, action potentials in these fibers remained difficult to elicit and were of low amplitude when compared with action potentials from control innervated and denervated fibers (Fig 2D–F). Many fibers remained inexcitable after treatment with 9-AC, despite the resultant high specific membrane resistance. In those that regained regenerative responses, the peak potential reached by action potentials was less at all resting potentials than the peak from comparable denervated fibers (data not shown).

We measured sodium content of lysate from control, denervated, and S-D muscle. Using published values of mammalian muscle intracellular sodium and potassium (Na = 12 mM; K = 155 mM),35 we calculated that in normal muscle more than 90% of the ions we measured had originated from the intracellular compartment, suggesting that we would be able to detect significant increases in intracellular sodium concentration. Through modeling of action potentials we estimate that the sodium equilibrium potential would have to drop to ~0 mV to eliminate regenerative membrane responses (Rich MM, Pinter MJ, unpublished data), corresponding to a 10-fold increase in intracellular sodium concentration. We found no evidence of differences in intracellular sodium between denervated (Na = 14.0 ± 4.3 mM) and S-D muscles (Na = 20.8 ± 3.6 mM, p = 0.3) large enough to produce a shift in the sodium equilibrium potential of this magnitude.

To determine whether a decrease in the number of sodium channels in S-D muscle might contribute to decreased excitability, we quantitated the density of adult isoform sodium channels (skeletal muscle type 1 [SkM1]) in sarcolemma purified from each of the four treatment groups. Saxitoxin (STX) binds with high affinity to the SkM1 sodium channel and has been used previously to quantitate these sodium channels in muscle.35 In control muscle, sodium channel density was 6.6 pM STX binding/mg of protein. This decreased slightly to 5.3 pM/mg protein after denervation (p < 0.05, Fig 4), consistent with our earlier measurements.35 After steroid treatment, the channel density decreased to 2.8 pM/mg of protein in innervated muscle (p = 0.001) and 3.4 pM/mg of protein in S-D

### Table 2. Muscle Excitability and Passive Membrane Properties before and after Chloride Channel Block

<table>
<thead>
<tr>
<th></th>
<th>Control Denervated Pre-9-AC</th>
<th>Steroid Denervated Pre-9-AC</th>
<th>Control Denervated Post-9-AC</th>
<th>Steroid Denervated Post-9-AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibers with AP</td>
<td>27/30</td>
<td>0/19</td>
<td>36/36</td>
<td>22/39</td>
</tr>
<tr>
<td>Resting potential (mV)</td>
<td>−60.8 ± 1.4</td>
<td>−59.3 ± 1.2</td>
<td>−60.7 ± 1.2</td>
<td>−62.5 ± 3.4</td>
</tr>
<tr>
<td>Input resistance (MΩ)</td>
<td>0.78 ± 0.14</td>
<td>0.88 ± 0.16</td>
<td>1.18 ± 0.17</td>
<td>1.97 ± 0.35</td>
</tr>
<tr>
<td>Radius (μm) of recorded fibers</td>
<td>22.6 ± 3.1</td>
<td>16.2 ± 1.6</td>
<td>23.3 ± 3.3</td>
<td>16.1 ± 1.9</td>
</tr>
<tr>
<td>Membrane resistance (Ω cm²)</td>
<td>2.915 ± 1.030</td>
<td>1.800 ± 1.005</td>
<td>7.355 ± 1.678</td>
<td>7.607 ± 2.312</td>
</tr>
<tr>
<td>Time constant (msec)</td>
<td>5.23 ± 0.52</td>
<td>4.16 ± 0.41</td>
<td>15.54 ± 1.09</td>
<td>16.49 ± 2.24</td>
</tr>
</tbody>
</table>

*Passive membrane properties of control denervated and S-D fibers before and after treatment with 25 μM anthrocene 9-carboxylic acid (9-AC).
Fig 2. Response to intracellular stimulation is shown for representative fibers from control innervated (A), control denervated (B), and S-D muscle (C). Recordings from three S-D fibers are shown after treatment with 9-AC (D–F). The control innervated fiber (A) had a resting membrane potential (RMP) of −79 mV at the time of stimulation and an action potential that peaked at +35 mV. The denervated control fiber (B: RMP = −57 mV) also had an easily elicited action potential. No action potential was obtained in the S-D fiber (C: RMP = −57 mV) despite 15-msec current pulses that depolarized the fiber 30 mV. In some S-D fibers after 9-AC exposure, action potentials were still absent (D: RMP = −57 mV) despite a high membrane resistance. In other 9-AC treated S-D fibers, a small local response was observed (E: RMP = −54 mV). Some fibers did give rise to small action potentials after 9-AC (F: RMP = −59 mV). In D and E, the largest depolarizing stimulus activated voltage-gated potassium channels, leading to after-hyperpolarization, despite the absence of action potentials. The after-hyperpolarizations seen in D, E, and F are accentuated by the block of chloride channels in these fibers. Two subthreshold stimuli are shown in each trace for comparison to the action potential.

Discussion
Concurrent corticosteroid treatment and denervation of skeletal muscle in rats appears to be a useful model of human AQM. This model re-creates key factors associated with weakness in most AQM patients, who typically receive high-dose corticosteroids during a period when they are paralyzed with nondepolarizing neuromuscular blocking agents. Neuromuscular blocking agents block voluntary muscle activation and produce all of the changes in muscle fiber properties observed after nerve section.37–62 Specifically, inactivity of muscle produced either through neuromuscular block or through nerve block results in a decrease in resting potential,37,38,42 an increase in specific membrane resistance,37,42 reappearance of TTX resistant (SkM2) sodium channels,38,42 and spread of acetylcholine sensitivity over the surface of the fiber.40–42 The combination of functional denervation and corticosteroid treatment results in loss of action potentials from a large percentage of fibers in both the animal model and human AQM, and the pathology seen in the animal model closely resembles that seen in patients.34,48–52 We found three factors in S-D rat muscle that may contribute to the reduced excitability of affected fibers: (1) denervation-induced reduction in resting potential, (2) lack of postdenervation down-regulation of G<sub>Cl</sub>, and (3) an apparent reduction in sodium conductance.

After denervation, one of the earliest changes in membrane properties is a 20-mV depolarization of the RMP, from approximately −80 mV to −60 mV, which may be secondary to reduced electrogenic contribution from the sarcolemmal Na<sup>+</sup>-K<sup>+</sup> ATPase.32,34,43 Because steady-state sodium channel inactivation is voltage dependent, this persistent depolarization will reduce the fraction of sodium channels available for activation, thereby decreasing peak inward sodium current amplitude.44–47 In normal denervated muscle, this is partially offset by a reduction in sarcolemmal G<sub>Cl</sub>, which increases membrane resistance and amplifies the local potential change produced by the remaining inward sodium current.26,51

It has previously been suggested that glucocorticoid treatment can lead to loss of excitability of innervated muscle by decreasing the RMP, which in turn inacti-
Fig 3. Action potential peak potential plotted versus resting potential at the time of stimulation. Control innervated fibers have the most negative resting potential, and the peak of the action potential was between +20 and +40 mV (○). Denervated control fibers are more depolarized and have action potentials that peak between 0 and +30 mV (□). S-D fibers from mildly affected muscle in which fibers were still excitable had decreased action potential peaks despite in three cases having resting potentials lower than −67 mV (●). In S-D fibers from severely affected muscle that had regenerative responses, action potentials peaked between −50 and −5 mV (○). Action potentials in S-D muscle still peaked at negative potentials despite reduction of leak by block of resting chloride conductance with 9-AC (△).

The combination of steroid treatment with denervation results in a loss of excitability of most fibers. Steroid treatment did not alter the decrease in RMP observed after denervation; inexcitable S-D muscle had resting potentials indistinguishable from denervated muscle with normal excitability. Steroid treatment did block the postdenervation increase in specific membrane resistance by preventing the expected decline in sarcolemmal G_{Cl}. However, even when excitability was partially restored in S-D muscle by blocking G_{Cl}, action potential amplitudes remained reduced, indicating a reduction in sodium current. Because the reduction in sodium current is not primarily due to a decrease in the sodium equilibrium potential, a decrease in sodium conductance is implicated.

One reason for a decrease in sodium conductance might be a decrease in total number of sodium channels present in affected muscle. We found evidence for a reduction in the density of SkM1 sodium channels in sarcolemma after steroid treatment in both innervated and denervated muscle, whether normalized to total membrane protein or cholesterol. However, the total sodium channel density in S-D muscle remains unknown because the number of SkM2 channels (TTX-resistant embryonic channels that are expressed after denervation) cannot be measured by saxitoxin binding assays. After denervation, these channels upregulate and eventually contribute 25 to 30% of the total sodium conductance. Even if SkM2 channel density is normal in S-D muscle, the decrease in SkM1 channel density would result in an overall sodium channel density less than that in denervated controls. It thus appears likely that a decrease in the density of sodium channels contributes to the reduced excitability of S-D muscle.

Is the observed combination of membrane depolarization, decreased number of SkM1 sodium channels, and maintained membrane leak enough to explain the loss of action potentials in S-D muscle? Because denervated fibers are depolarized to a similar degree as S-D fibers, the difference in sodium current cannot simply reflect depolarization-induced channel inactivation. The decrease in number of SkM1 channels we measured might be sufficient to lead to loss of action potentials when combined with denervation-induced depolarization if SkM2 channels are decreased to a similar degree. It is also possible, however, that there is an alteration in sodium conductance in S-D muscle that is not explained by a decrease in number of so-
tude and mechanism of the reduction in sodium elec-
trical excitability in many fibers. Three changes in
that normally occurs after denervation, and which leads
to increased sodium channel inactivation. The second
is the persistent expression of chloride conductance in
the sodium channel. Which increases leak. The third is a redu-
tion in sodium conductance, which may be secondary,
part to a decreased density of sodium channels.

In summary, we found that steroid treatment of
denervated rat muscle, as in humans, results in loss of
electrical excitability in many fibers. Three changes in
properties appear to contribute to this loss of
 excitability. The first is the depolarization of the RMP
which normally occurs after denervation, and which leads
to increased sodium channel inactivation. The second
is the persistent expression of chloride conductance in
S-D muscle, which increases leak. The third is a reduc-
tion in sodium conductance, which may be secondary,
in part, to a decreased density of sodium channels.
Further studies are necessary to determine the magni-
tude and mechanism of the reduction in sodium conduc-
tance.

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