Spatial Distribution of Fiber Degeneration in Acute Hypoglycemic Neuropathy in Rat

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Abstract. Hypoglycemia may cause axonal nerve fiber degeneration, but to do so it must be severe (<1.5 mmol/L) and of long duration (>24 hours). Since in our previous study, systemic PO₂, PCO₂, pH, blood pressure, temperature, and hematocrit were maintained within physiologic limits, fiber degeneration cannot be attributed to systemic hypoxia. In this study the spatial distribution of axonal degeneration was assessed in transverse epoxy sections and teased fibers from different proximal-to-distal levels of nerves of the lower limb of the rats. Reactions in lumbar spinal motor neurons, spinal ganglia, and fasciculus gracilis were also studied. Axonal degeneration was the characteristic fiber alteration and it predominated in central fascicular distributions of distal sciatic, proximal tibial, and proximal peroneal nerves. This proximal-to-distal and central fascicular spatial distribution is not typical of distal polyneuropathy or of neuronal degeneration, but it is characteristic of a focal or multifocal nerve trunk neuropathy. Although local hypoxic-ischemic injury, possibly mediated by enhanced sympathetic tone, has not been excluded, we postulate a generalized deficiency of energy substrate manifesting itself by fiber degeneration at watershed zones of poorest perfusion.

Key Words: Energy substrate deficiency; Hypoglycemia; Insulin; Nerve degeneration; Neuropathy; Watershed zones of poor nerve perfusion.

INTRODUCTION

Prolonged severe hypoglycemia may cause damage of the central nervous system (CNS) and peripheral nervous system (PNS) in humans (1–7) and in experimental animals (8–10). Decreased energy substrate and altered axonal transport may be involved in causing this damage (11, 12). The spatial distribution of the structural alteration in the PNS is unresolved (9, 11). Some investigators have suggested preferential injury of motor neuron somas (2, 3), and others have suggested involvement of peripheral nerves (4, 5, 9).

To study the effect of hypoglycemia on peripheral nerves, we developed a model in which the degree and the duration of a single period of hypoglycemia could be varied and hypoglycemia could be maintained for times up to 18 hours (h) (10). The systemic blood pressure, PO₂, PCO₂, blood pH, temperature, and hematocrit were maintained within physiologic limits by pentobarbital anesthesia, mechanical ventilation, temperature control, and attention to fluid balance. The frequency of axonal degeneration was related not only to duration and severity of hypoglycemia but also to immaturity of the rats.

In the present study we assessed the spatial distribution of fiber degeneration in proximal-to-distal levels of peripheral nerves and different levels of fasciculus gracilis and pathologic alteration of somas of lumbar motor neuron columns and of spinal ganglia neurons. Results showed that the central fascicular region at the mid-thigh...
level (distal sciatic, proximal tibial, and proximal common peroneal nerves) was especially vulnerable.

MATERIALS AND METHODS

Animals

The peripheral nerves, spinal ganglia, and spinal cords studied were from the 15 young male Sprague-Dawley rats (mean weight ± SEM, 274 ± 9 g) of our previous study (10). In brief, under pentobarbital anesthesia, endotracheal intubation, and mechanical ventilation, hypoglycemia was induced in nine rats by intravenous insulin injection (4.5 U/kg body weight, Iletin II, Eli Lilly and Co., Indianapolis, IN); thereafter, intermittent insulin injections were administered subcutaneously (0.3 U/kg) to maintain plasma glucose at levels averaging <1.5 mmol/L for 12 to 18 h. The six control rats, similarly anesthetized and ventilated, were given bacteriostatic water (Travenol Laboratories, Deerfield, IL) instead of insulin. In both groups, body temperature, PO₂, PCO₂, blood pH, arterial blood pressure and hematocrit were maintained within physiologic limits (10). Recovery after hypoglycemia was induced by withholding insulin and giving dextrose into the stomach. At hourly intervals, blood samples were taken from a tail vein and plasma glucose was measured by a glucose oxidase method (Beckman Glucose Analyzer 2, Beckman Instruments, Fullerton, CA).

Histologic Studies

One week after the acute experiment and under pentobarbital anesthesia rats were perfused through the heart with 2% glutaraldehyde and 2% paraformaldehyde in 0.05 M cacodylate buffer at pH 7.38, warmed to 37°C.

In the nine anesthetized and mechanically ventilated hypoglycemic rats and in the six anesthetized and mechanically ventilated normoglycemic rats, the right fifth lumbar dorsal and ventral spinal root, proximal and distal sciatic nerve, tibial nerve, common peroneal nerve (proximal and distal segments), and superficial peroneal nerve (proximal and distal segments) were removed and histologically processed for study of teased fibers and for study of semithin epoxy sections stained with 1% methylene blue and 1% paraphenylenediamine.

For preparation of teased fibers, 8-mm lengths of nerves (11 from proximal-to-distal levels of spinal roots and nerves) were cut, washed, osmicated, glycerinated, and teased by methods previously described (13). At least 100 fibers per segment of nerve were prepared and the frequency of teased fiber abnormalities was calculated. In brief, the teased fiber conditions are: A = normal, B = myelin wrinkling, C = demyelination, D = demyelination and remyelination, E = axonal degeneration, F = remyelination, and G = focal myelin reduplication.

For microscopic study, three consecutive 2-mm lengths of spinal roots and nerves (listed above, 12 proximal-to-distal levels from each of 15 rats) were cut, postfixed in 2% osmium tetroxide for 2 h, and embedded in epoxy. Transverse (from the first and third blocks) and longitudinal (from the second block) semithin (1 μm) sections were cut from consecutive blocks and stained with 1% methylene blue and 1% phenylenediamine. The ultrathin sections from the epoxy-embedded blocks of the distal sciatic, proximal tibial, and proximal common peroneal nerves of the rat—e.g. the rat that was hypoglycemic for 18 h—with the highest frequency of fiber degeneration were stained with uranyl acetate and lead citrate and viewed in a Philips 300 electron microscope.

To study the light microscopic alteration of somas of motor neurons, of spinal ganglia, and of proximally directed myelinated fibers of fasciculus gracilis, semithin (1 μm) epoxy sections stained with methylene blue were studied from the three most severely affected (highest percent of teased fibers undergoing axonal degeneration) hypoglycemic (12, 13, and 18 h) rats and from three age- and weight-matched, mechanically ventilated (14 h) normoglycemic rats. For study of alteration of the L-5 spinal ganglia somas, five serial skip (every 50 μm) sections from these six rats were studied. For study of alteration of L-5 motor neuron somas (medial and lateral groups), five serial skip (every 50 μm) sections of the same six rats were studied. For study of alteration of fasciculus gracilis myelinated fibers, five serial skip (every 50 μm)
TABLE 1
Number, Age, Body Weight, Duration of Experiments, and Plasma Glucose Level of Hypoglycemic and Control Rats*

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age (weeks)</th>
<th>Body weight (g)</th>
<th>Duration (h)</th>
<th>Plasma glucose, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemic</td>
<td>9</td>
<td>8.3 ± 0.5</td>
<td>272 ± 12</td>
<td>13.4 ± 0.6 (12–18)</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>Control (mechanically ventilated)</td>
<td>6</td>
<td>8.7 ± 0.3</td>
<td>279 ± 4</td>
<td>13.0 ± 0.5 (12–14)</td>
<td>4.1 ± 0.2†</td>
</tr>
</tbody>
</table>

* The results are expressed as mean ± standard error of the mean. Range is in parentheses.  † Statistical significance (Student's two-sample t-test): † = p < 0.001.  
  n = Number of rats.

sections of tissue blocks from each of C-1, C-4, D-1, D-4, D-8, L-1, and L-5 segmental levels of each of the six rats (three hypoglycemic and three control) were studied. The L-5 segment of the spinal cord and spinal ganglion was selected because it is a major source of the sciatic nerve in rat (14). In sections of spinal cord or spinal ganglia we assessed somas of motor neuron columns and spinal ganglia for degeneration or for an axon reaction (15). The criteria for an axon reaction are those of Jones and Cavanagh (16): a) eccentric nucleus, b) nuclear membrane crenated, c) peripheral distribution of Nissl substance, and d) more than ten enlarged mitochondria. Only somas with a nucleolus were used for this assessment.

Data Analyses

Values are given as means ± standard error of the mean (SEM).

Statistical differences between mean values of teased fiber abnormalities among experimental groups were compared with Student's two-sample t-test, using two tails and a confidence interval of 95%.

The differences between percent of L-5 spinal ganglion somas showing an axon reaction in a rat hypoglycemic for 18 h and three normoglycemic rats for 14 h were compared using Chi square analysis.

RESULTS

The number, age, body weight, and duration and severity of glycemic control of the two groups of rats are summarized in Table 1. Hypoglycemia, averaging less than 1.5 mmol/L, was maintained for more than 12 h in the hypoglycemic group.

Teased Fibers

The only type of teased fiber abnormality that was significantly more frequent in hypoglycemic than in normoglycemic rats was axonal degeneration (Table 2). Although remyelination was on average more frequent in teased fibers of hypoglycemic rats, it did not reach statistical significance. The mean frequency (± SEM) of axonal degeneration was higher in the hypoglycemic than in the normoglycemic group of rats mainly at mid-thigh levels of nerves: distal sciatic (4.2 ± 1.6% vs 0.2 ± 0.2%, p < 0.05); proximal common peroneal (6.6 ± 1.6% vs 0.5 ± 0.2%, p < 0.02); distal common peroneal (4.2 ± 1.3% vs 0.2 ± 0.2%, p < 0.05) and proximal tibial (7.7 ± 2.8% vs 0.3 ± 0.2%, p < 0.05) nerves. For distal nerves, evaluated frequencies of fiber degeneration were generally higher in hypoglycemic than in normoglycemic rats but usually did not reach statistical significance: distal common peroneal (see above), distal tibial (3.2 ± 1.8% vs 0.2 ± 0.2%, p > 0.05) and distal superficial peroneal (0.0 ± 0.0% vs 0.0 ± 0.0%, p > 0.05). In roots and proximal nerve,
**TABLE 2**

Frequency of Graded Teased Fibers From Various Levels of Hypoglycemic and Control Rats

<table>
<thead>
<tr>
<th>Proximal-to-distal nerve levels</th>
<th>Hypoglycemic</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>A</td>
</tr>
<tr>
<td><strong>Dorsal root</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>9</td>
<td>99.3 ± 0.2</td>
</tr>
<tr>
<td>Distal</td>
<td>9</td>
<td>99.6 ± 0.3</td>
</tr>
<tr>
<td><strong>Ventral root</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>9</td>
<td>99.6 ± 0.2</td>
</tr>
<tr>
<td>Distal</td>
<td>7</td>
<td>99.3 ± 0.4</td>
</tr>
<tr>
<td><strong>Sciatic nerve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>9</td>
<td>95.3 ± 1.6</td>
</tr>
<tr>
<td><strong>Tibial nerve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>9</td>
<td>92.0 ± 2.7</td>
</tr>
<tr>
<td>Distal</td>
<td>9</td>
<td>96.8 ± 1.8</td>
</tr>
<tr>
<td><strong>Common peroneal nerve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>9</td>
<td>92.9 ± 1.7</td>
</tr>
<tr>
<td>Distal</td>
<td>5</td>
<td>95.4 ± 1.3</td>
</tr>
<tr>
<td><strong>Superficial peroneal nerve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>7</td>
<td>100.0 ± 0.0</td>
</tr>
<tr>
<td>Distal</td>
<td>9</td>
<td>100.0 ± 0.0</td>
</tr>
</tbody>
</table>

* Abbreviated description of teased fiber abnormalities: A = normal; E = axonal degeneration; F = remyelination. Conditions B (myelin wrinkling), C (demyelination), D (demyelination and remyelination), and G (focal myelin reduplication) were not observed in either hypoglycemic or control rats.

† Statistical analysis done by Student's two-sample t-test; NS = not significant (p > 0.05). SEM = standard error of the mean.

n = number of nerves.
FIBER DEGENERATION IN HYPOGLYCEMIC NEUROPATHY

Fig. 1. Proximal-to-distal spatial distribution of axonal degeneration % of fibers showing change (Condition E) in teased fibers from rats hypoglycemic for 12, 13, and 18 h seven days after experiments.

frequencies of fiber degeneration did not reach statistical significance: in L-5 proximal ventral spinal root (0.2 ± 0.2% vs 0.2 ± 0.2%, p > 0.05) and L-5 distal dorsal root (0.3 ± 0.2% vs 0.2 ± 0.2%, p > 0.05).

Semithin Sections of Peripheral Nerve

For many nerves of hypoglycemic rats, axonal degeneration did not occur frequently enough to be able to make judgments about spatial distribution of fiber degeneration from evaluation of transverse sections at a given level. Therefore, we focused on the three hypoglycemic rats showing the highest frequencies of fiber degeneration (12, 13, and 18 h) (Fig. 1). In these rats, degenerating fibers were restricted to central fascicular regions of the proximal tibial nerves in two of three rats, of the distal sciatic nerves in three of three rats, and of proximal common peroneal nerves in two of three rats (Fig. 2). In one proximal tibial nerve, one

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Control rat</th>
<th>12-hour hypoglycemic rat</th>
<th>13-hour hypoglycemic rat</th>
<th>18-hour hypoglycemic rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal sciatic</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Distal sciatic</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Proximal common peroneal</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Proximal tibial</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Distal tibial</td>
<td>.</td>
<td>.</td>
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</tr>
</tbody>
</table>

Fig. 2. Drawings of transverse semithin epoxy sections of proximal and distal sciatic, proximal common peroneal, proximal and distal tibial nerves of a control mechanically ventilated for 14 h and rats hypoglycemic for 12, 13, and 18 h seven days after experiments. Degenerating fibers and “attenuated axon” are indicated by dots. Note central fascicular fiber degeneration in most nerves at mid-thigh level. The proximal sciatic nerves of hypoglycemic rats did not show abnormal frequencies of fiber degeneration beyond what was seen in a control rat.

proximal common peroneal nerve, and three distal tibial nerves, fiber degeneration was demonstrated in both central fascicular and subperineurial regions. Proximal sciatic nerves did not show abnormal rates of fiber degeneration beyond what was found in control rats (Fig. 2). In affected regions axonal degeneration, dark axons, and attenuated (small caliber relative to myelin thickness) axons were encountered (Fig. 3).

No abnormality was observed in the superficial peroneal nerves or dorsal and ventral roots.

**L-5 Spinal Cord and Spinal Ganglia and Fasciculus Gracilis**

Occasionally, somas of motor neuron columns and of spinal ganglia of hypoglycemic rats demonstrated peripheral Nissl substance and eccentric nuclei, indicating central chromatolysis in the rat hypoglycemic for 18 h (Table 3 and Fig. 4). Somal degeneration was not observed.

Occasionally, degenerating myelinated fibers in fasciculus gracilis were encountered at various levels (C-1 to L-5) of the spinal cord of rat hypoglycemic for 18 h, but it was not more frequent than in controls.

**Electron Microscopic Study of Nerves**

The degenerating fibers with myelin debris or myelinated fibers with "attenuated axons" observed under the light microscope were the most frequent abnormal features under the electron microscope in the rat hypoglycemic for 18 h. Myelinated fibers with "attenuated axons" were observed with axons filled with accumulated

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**Fig. 4.** Left: Lower motor neurons of anterior horn of right fifth lumbar enlargements from a rat hypoglycemic for 18 h (A) and a rat that was mechanically ventilated for 14 h (B). Peripheral Nissl substance is seen (arrow) in a rat hypoglycemic for 18 h. Right: Neuron cell bodies of right fifth lumbar dorsal root ganglia from a rat hypoglycemic for 18 h (C) and a control rat that was mechanically ventilated for 14 h (D). Peripheral Nissl substance is seen (arrows) but neuronal cell death is not demonstrated in a rat hypoglycemic for 18 h. Bars = 50 µm.

**Table 3**

<table>
<thead>
<tr>
<th>Cells studied</th>
<th>n</th>
<th>Eccentric nucleus, %</th>
<th>Nuclear membrane crenated, %</th>
<th>Peripheral Nissl substance, %</th>
<th>&gt;10 enlarged mitochondria, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal root ganglion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0.4 ± 0.3</td>
<td>0</td>
</tr>
<tr>
<td>18 h hypoglycemic</td>
<td>1</td>
<td>0 (0/222)</td>
<td>0 (0/222)</td>
<td>2.7 (6/222)*</td>
<td>0 (0/222)</td>
</tr>
<tr>
<td>Anterior horn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18 hr hypoglycemic</td>
<td>1</td>
<td>0.9 (1/110)</td>
<td>0 (0/110)</td>
<td>1.8 (2/110)</td>
<td>0 (0/110)</td>
</tr>
</tbody>
</table>

The results are expressed as mean ± standard error of the mean.

Classification of abnormalities in neuron cell bodies was done in accordance with the description by Jones and Cavanagh (16). A total of 216 to 229 cells from each ganglion and 75 to 124 cells from each anterior horn of the right side of the spinal cord were studied in the three control rats. Statistical analysis was done by χ² test.

* = p < 0.01.
organelles, myelin debris, separation of the inner myelin lamella, or hypermyelination. "Dark axons" filled with accumulated organelles were occasionally demonstrated. "Dark axons with light cores," "tubular" or "honeycomb profiles," or "de-myelinated axons" were not observed.

DISCUSSION

The spatial distribution of pathologic alterations from hypoglycemia has been extensively studied in brain (17-19). Rosner and Elstad (5), reviewing previous clinical observations, autopsy data, and experimental models, suggested that glucose lack, if severe enough, induces graded effects in various anatomic regions of the nervous system. However, in nerve the spatial distribution of hypoglycemic injury has not been studied extensively (11, 20). Also, in most previous studies mechanical ventilation and constant surveillance were not used to ensure that hypoxia was not the explanation for the neuropathy.

Sidenius and Jakobsen (8) found axonal degeneration in the sciatic and tibial nerves and chromatolysis of lumbar motor somas in rats made hypoglycemic with insulin during a 72 h period. Recently Dyer and Messing (9), studying SV40 transgenic mice with functional islet cell adenomas and spontaneous hypoglycemia, reported axonal degeneration in the sciatic, common peroneal branch of tibial nerve to calf muscles, distal ventral spinal root, and dorsal columns of the spinal cord. Degeneration was not found in the distal tibial, distal sural, proximal ventral spinal root, lumbar motor neurons, or sensory ganglia. Large diameter myelinated fibers were reported to be preferentially affected. They postulated a dying back neuropathy with progression to the level of the proximal axon, but they may not have studied sufficient levels to answer the question adequately. In the last two studies cited, assessment of the duration and severity of hypoglycemia was only approximate and the occurrence of episodes of hypoxia cannot be excluded.

In our recent study (10), the degree and duration of hypoglycemia was known. In addition, since mechanical ventilation had been employed and PO2, Pco2, pH, and hematocrit had been evaluated at periodic intervals, nerve injury could not be explained by systemic hypoxia.

In the present study we found that: 1) axonal degeneration was the characteristic abnormality of teased fibers; 2) increased frequency of axonal degeneration occurred only in distal sciatic, proximal tibial, and common peroneal nerves, but not in dorsal and ventral spinal roots, distal tibial and superficial peroneal nerves, or in fasciculus gracilis; 3) fiber degeneration occurred especially in "central fascicular" regions in distal sciatic, proximal tibial, and proximal peroneal nerves; 4) occasional lumbar motor neuron somas demonstrated central chromatolysis but not neuronal cell death; and 5) in axons of fasciculus gracilis degeneration was not demonstrated beyond the frequency observed in controls. Thus, the major site of the nerve damage in our hypoglycemic rats was the axon, especially in the mid-thigh level of distal sciatic and proximal tibial and peroneal nerves. Even though the changes were not as severe as those encountered after ischemic injury induced by multiple arterial ligation (21-23) or microsphere embolization (24, 25), the spatial distribution of fiber injury bears a striking resemblance to that encountered in ischemic injury (21, 25-27).

The three patterns of neuronal (axonal) injury we considered to explain our findings were: 1) neuronal degeneration, 2) dying back neuropathy, and 3) nerve trunk focal or multifocal neuropathy. Our findings do not support the concept of neuronal degeneration for the following reasons: 1) neuronal somas showed only reactive changes, not degeneration, 2) the frequency of fiber degeneration in ventral or dorsal
roots was not higher than in controls, 3) fasciculus gracilis did not show a higher than normal frequency of degenerating fibers, and 4) peripheral nerve fiber degeneration was significantly higher only for mid-thigh levels.

Our findings also do not appear to support a dying back process: 1) a distal-to-proximal gradient of fiber degeneration was not found and 2) the highest frequency of degenerating fibers occurred at the mid-thigh level, not distally. We considered the possibility that the distribution of degenerating fibers could represent a distal fiber degeneration of muscular or cutaneous branches of sciatic nerve. While a survey of sciatic branches was not undertaken, we consider this possibility less likely than the one we propose for three reasons: 1) the central fascicular distribution of degenerating fibers is unlike that of branch fibers which assume a position near the periphery, 2) the affected proximal-to-distal levels of nerve, shown to have the highest frequency of degenerating fibers, have no or few branches, and 3) the frequency and distribution of degenerating fibers, in distal levels of nerve, is as expected.

Our findings are more in keeping with a focal (usually central fascicular) involvement of nerve trunks with special vulnerability of fibers at mid-thigh levels. Several mechanisms might be considered: 1) insufficiency of energy substrate, 2) local nerve ischemia, 3) failure of axonal transport due to 1 or 2, and 4) other mechanisms.

Because the kind (axonal degeneration) and distribution (mid-thigh level and central fascicular distribution) of effects are so similar to those found in experimental hypoxic-ischemic injury (21, 23, 24), two major mechanisms have to be considered. Assuming a generalized depletion of energy substrate, regions of poorest vascular perfusion might be most vulnerable (21, 24, 28–31). Although most macromolecules are synthesized in the perikaryon, oxygen and energy substrate are locally supplied. Presumably the endoneurial microenvironment and nerve fibers contain sufficient energy substrate (32–34) so that even with acute energy substrate deficiency, no failure occurs for many hours. After approximately 12 hours the available energy substrate may become depleted and is not sufficient for cellular needs. It is perhaps not surprising that it first occurs in watershed zones of poorest perfusion. Assuming generalized energy substrate deficiency, fast axonal transport might fail in regions receiving the least amounts of substrate. Sidenius and Jakobsen (8, 11, 12) reported somewhat contradictory alterations of axonal flow in hypoglycemic nerve injury. From our studies, it appears that axonal transport would have to be studied after many hours of hypoglycemia and in individual fibers to reveal its role in fiber degeneration.

The second possibility to explain the type and distribution (24) of fiber injury is local nerve ischemic injury. Because we mechanically ventilated rats and know that systemic oxygen tension was maintained for the duration of the experiments, one might assume that hypoxia of the nerve microenvironment had not occurred. Because oxygen tension and blood flow were not actually measured locally at the nerve bed, we cannot be certain that local microhypoxia of sufficient severity to cause injury did not occur. Conceivably, alteration in blood flow could be induced by abnormalities of rheology (35–38), shunting, or other mechanisms. One mechanism, assuming local decrease of blood flow to nerve, that might be considered is vasoconstriction of epineurial arterioles (39–41). Conceivably, this could be induced by hypoglycemia, through increase of plasma catecholamines (42–44) acting on α-adrenergic receptors (45–48), thus inducing vasoconstriction of epineurial blood vessels (39–41, 49).

Do excitatory amino acids (or excitatory neurotoxins) play a role in the induction of hypoglycemic neuropathy as postulated for CNS (50–54)? Because these excitatory
amino acids are thought to preferentially affect dendrites and somas but not axon trunks of nerve (55, 56), it seems unlikely that peripheral nerves would be damaged by this mechanism.

We hypothesize that hypoglycemic nerve injury is due to energy substrate insufficiency manifesting itself first in regions of poorest perfusion.

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