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Local Anesthetic-induced Conduction Block and Nerve Fiber Injury in Streptozotocin–Diabetic Rats

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Patients with diabetes may have peripheral neuropathy, which may have clinical implications for the use of regional nerve block. The effects of local anesthetics on nerve conduction and nerve fiber injury were tested in control rats and at 4 weeks after the onset of diabetes in rats injected with streptozotocin (50 mg/kg intraperitoneally). Nerve conduction was assessed by recording evoked electrical activity in hindpaw muscles following ipsilateral electrical stimulation of the sciatic nerve near the hip. Block of motor nerve conduction was quantified by recording the amplitude of the evoked response at 1-min intervals for up to 15 min after the injection of 500 μl 1% lidocaine HCl or procaine HCl into the midthigh next to the sciatic nerve. In control animals, procaine was much less effective than lidocaine in producing conduction block. The rate and magnitude of lidocaine-induced conduction block were not significantly different between control and diabetic groups. However, conduction block due to procaine was sufficiently enhanced in diabetic rats to become comparable to that of lidocaine-treated control nerves. Long-lasting injury was assessed in sciatic nerve harvested 2 days after the extraneural injection of saline or 2 or 4% lidocaine HCl. Using a light microscope with a superimposed grid, nerve edema was quantified as the proportion of intersection points falling on extracellular space. Lidocaine induced edema in both control and diabetic nerves, but 4% lidocaine induced significantly more edema in diabetic nerves than in controls. Nerve fiber injury, based on light microscopic scoring of axonal degeneration and demyelination, was not observed in saline-treated nerves. Injury was evident in all lidocaine groups and was significantly greater for lidocaine-treated diabetic nerves compared to lidocaine-treated controls. These data support the proposals that, in diabetes, local anesthetic requirement is reduced and that the risk of local anesthetic–induced nerve injury is increased. (Key words: Anesthetics, local: lidocaine; procaine. Diabetes: streptozotocin. Nerve: peripheral.)

A SUBSTANTIAL PROPORTION of diabetic patients[1] have clinical or subclinical neuropathy, which may present special concerns for the use of local anesthetics. Before the onset of pain, paresthesias, or sensory loss, diabetic neuropathy can remain undetected without electrophysiologic testing for slowing of nerve conduction velocity.[2] This underlying nerve dysfunction, in combination with diabetes-associated microangiopathy of peripheral nerve blood vessels,[3,4] provides a basis for the hypothesis that patients with diabetes have a reduced requirement for local anesthetic.[5] It is possible that impaired nerve conduction in diabetic patients requires less anesthetic to produce anesthesia; in addition, microvascular disease, resulting in impaired nerve blood flow,[6,7] may reduce the rate at which anesthetic distributes away from the site of administration.

It has been proposed that the combination of diabetes and an otherwise safe dose of anesthetic might result in nerve injury.[8] High doses of local anesthetic have been reported to induce nerve fiber injury[9–11] and to reduce nerve blood flow, suggesting that the lesion is ischemic in origin.[12] Fibers in diabetic nerve may therefore be more susceptible to anesthetic toxicity both because they are exposed to a higher local concentration of anesthetic due to impaired blood flow and because they are already stressed by chronic ischemic hypoxia. However, it can also be argued that the neurotoxic effects of local anesthetics might be *reduced* in diabetes. This possibility arises from the observation that both diabetic patients and animals with experimental diabetes are *resistant* to conduction block induced by ischemia or hypoxia.[13,14] Prolonged survival of diabetic nerve has been attributed to a shift to anaerobic glycolysis due to either the reduced energy requirement of diabetic nerve[15] or improved anaerobic metabolic processes in adaptation to chronic incipient ischemia.[16] Diabetic nerves may, therefore, be more able to resist local anesthetic–induced fiber damage caused by ischemia-associated hypoxia.

Neither clinical nor experimental testing of diabetes-associated changes in anesthetic potency and toxicity of local anesthetics has been reported. In this study, the possibility of such changes is addressed through electrophysiologic and histopathologic studies on nerves of control and streptozotocin-diabetic rats.

Materials and Methods

After approval by the Institutional Animal Care Committee, female Sprague-Dawley rats (250–280 g; Charles River) were randomly assigned to one of two groups. Rats of one group were fasted overnight before being made diabetic by intraperitoneal injection of streptozotocin (Sigma Chemical Co., St. Louis, MO) 50 mg/kg, freshly dissolved in sterile 0.9% NaCl. Three days later, the glucose concentrations of blood samples obtained by tail prick

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were measured using a glucose oxidase–impregnated test strip (Ames Glucostix, Myles Inc., Elkhart, IN). Streptozotocin-injected rats with a blood glucose concentration of < 15 mM were excluded from further experimentation. The remaining animals formed a control group that did not receive injections of streptozotocin but that otherwise was treated identically to the diabetic group. Both control and diabetic rats were maintained on wire cage bottoms for 4 weeks and then used for studies of local anesthetic–induced conduction block or nerve injury. Animals were prepared for surgical procedures by the intraperitoneal injection of 2 ml/kg pentobarbital (12.5 mg/ml) and diazepam (1.25 mg/ml); intraperitoneal supplements (0.1–0.2 ml) of these drugs were administered to maintain depth of anesthesia during surgery. After nerve conduction tests or the removal of nerves for histology, blood samples were taken to determine serum glucose levels by spectrophotometric assay (GOD-PERID glucose assay kit, Boehringer Corporation, London, U.K.).

ELECTROPHYSIOLOGY

Eight control and 12 diabetic rats were used in studies of motor nerve conduction block. Test solutions of 1% (37 mM) lidocaine HCl (Research Biochemicals Incorporated, Natick, MA) and 1% (37 mM) procaine HCl (Sigma Chemical Co.) were prepared in 0.9% saline on the day of testing. Control and diabetic rats each were tested using the left nerve for lidocaine and the right nerve for procaine. The choice of sequence for nerve testing (left or right) was random, and there was no evidence of differential effects based on sequence. After induction of general anesthesia, the left and right hindlimbs were shaved, and each sciatic nerve was exposed by cutting through overlying muscle tissue just posterior to the femur, in the midthigh region. A thermistor was placed between skin and muscle at the site of incision so that the temperature of the sciatic nerve could be monitored and maintained at 37° C by feedback to a temperature controller (Yellow Springs Instrument Co., Ohio) connected to a heat lamp. Electrical stimuli were produced by a PSIU6 constant current stimulus isolation unit (Grass Instruments Co., Quincy, MA) driven by a 50-V, 50-μs monophasic stimulus (58019 Square Wave Stimulator, Stoelting Co., Chicago, IL). This stimulus was supramaximal in control and diabetic rats, and, based on our previous experience, these stimulation parameters are also supramaximal in nerves treated with local anesthetic solutions.‡ The active stimulation electrode was inserted first at the ankle and then at the sciatic notch; a reference electrode was inserted into adjacent muscle tissue. Two EMG needle electrodes were inserted into the interosseous muscles of the lateral digits to obtain a bipolar recording referenced to a ground electrode located in the plantar surface of the ipsilateral foot. Evoked electrical activity of the foot muscles was amplified (× 100) with a P15 A.C. Amplifier (Grass Instruments Co., Quincy, MA) and recorded on a 5110 Storage Oscilloscope and 5D10 Waveform Digitizer (Tektronix, Inc., Beaverton, Oregon).

After verification that tissue temperature was 37° C, and before administration of local anesthetic solutions, motor nerve conduction velocity (MNCV) was derived by stimulation first at the ankle and then at the sciatic notch. To calculate MNCV, the distance between stimulation sites (measured by removing the nerve at the conclusion of the experiment) was divided by the difference in latency to the evoked motor response. Examples of traces from control and diabetic animals are shown in figure 1. With the stimulation electrode at the sciatic notch, repeated baseline measurements were made at 1-min intervals for at least five min to ensure that response amplitudes were within a range of ± 10% of the average and that the response was not decaying over time. Motor nerve conduc-

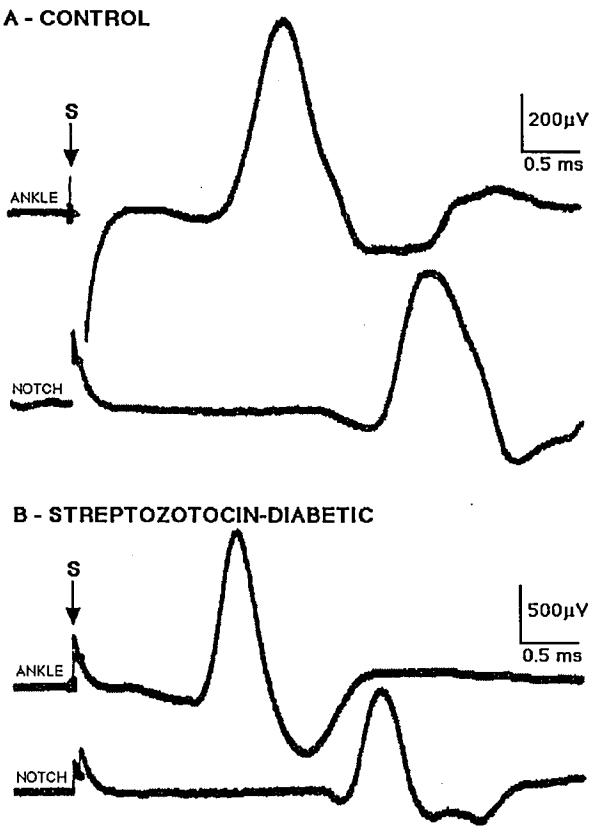

FIG. 1. Representative examples of recorded electrical activity of interosseous motor fibers secondary to electrical stimulation at the ankle and sciatic notch in control (*A*) and streptozotocin-diabetic (*B*) rats. Amplitude scale is for unamplified signal.

‡ Kalichman MW: Unpublished observations.

tion block was assessed after the injection of 500 μl of the local anesthetic test solution next to the sciatic nerve. Using a 30-G needle, each solution was injected in approximately equal volumes into the soft tissue on either side of the sciatic nerve. Measurements of response amplitude were made immediately after injection and subsequently at 1-min intervals for up to 15 min. Data points were excluded for two diabetic animals that died before the end of testing and for one nerve in which the drug injection had been made next to the peroneal branch of the sciatic nerve.

Histopathology

Eight control and eight diabetic rats were used for studies of local anesthetic–induced nerve injury. Using the procedures described above, the left and right sciatic nerves were exposed, and 500 μl 0.9% saline, 2% lidocaine HCl, or 4% lidocaine HCl was injected next to each nerve. Test solutions were coded to mask the identity of the agents being injected. After injections, the incisions were closed and the animals allowed to recover. After 2 days, the rats were anesthetized again, and a 1-cm length of nerve was removed for histologic processing. The nerves were immersion-fixed in 2.5% phosphate-buffered glutaraldehyde and processed by postfixation in 1% osmium tetroxide, dehydration in serial concentrations of ethanol and propylene oxide, and infiltration and embedding with araldite resin. From a 2-mm block taken from the center of each nerve, transverse sections (1 μm) were cut, transferred to slides, and stained with paraphenylenediamine for examination by light microscopy.

The coded slides were viewed by investigators unaware of either the test solutions or the experimental groups. Scores for edema and nerve fiber injury were verified by an investigator trained in neuropathology (MWK). The volume fraction of edema was estimated in the largest fascicle of each nerve using a light microscope with a final magnification of 200× and a camera lucida attachment to superimpose the image of a rectangular grid with magnified spacing equivalent to 90 μm between intersections. Grid intersections falling on extracellular space were taken as a measure of interstitial fluid. The amount of extracellular space was normalized by dividing by the number of intersection points falling on all other elements in the nerve fascicle. An increase over normal levels was considered to be consistent with nerve edema.

Nerve injury scores were derived for degeneration and demyelination of myelinated nerve fibers: no apparent injury (0); injury of as many as three fibers in any fascicle (1); injury of as many as a quarter of the fibers in any one fascicle (2); injury of as many as half of the fibers in any one fascicle or more than three fibers in two or more fascicles (3); and injury of more than half of the fibers in any one fascicle (4). Early axonal degeneration was recognized by abnormally darkly staining axoplasm. In subsequent stages, axonal disintegration was characterized by a swollen, vacuous profile and then by collapse of the myelin sheath. Demyelination, typically secondary to axonal degeneration, was evidenced by breakdown of the myelin sheath. The largest fascicle of the rat sciatic nerve has on the order of 5,000 nerve fibers.

Data Analysis

Other than the final statistical comparisons, all experimental and analysis procedures were performed with coded animals, tissue, and data to avoid investigator bias. Differences in body weight, serum glucose, and MNCV between the groups of control and diabetic rats were tested using an unpaired t test. The difference between local anesthetic–induced conduction block in control and streptozotocin-diabetic groups was tested with a two-factor repeated-measures analysis of variance. The volume fraction of edema was compared using a two-factor (dose of lidocaine: 0%, 2%, and 4%; group: control, diabetic) analysis of variance. Nerve fiber injury was compared by a two-factor (dose of lidocaine: 2%, 4%; group: control, diabetic) Kruskal-Wallis analysis of variance. Unless otherwise indicated, all values are mean ± SD.

Results

Serum glucose levels exceeded 15 mM in all streptozotocin-diabetic rats and were significantly ($P < 0.001$) greater than control values (control 9.9 ± 3.4 mM, diabetic 24.6 ± 5.2 mM). The final body weight of diabetic rats was significantly ($P < 0.001$) lower than controls (control 405 ± 22 g, diabetic 309 ± 33 g), and MNCV, determined only in animals used in the conduction block studies, was also lower in the diabetic rats (control 50.4 ± 5.0 m/s, diabetic 46.6 ± 5.5 m/s), although this did not attain statistical significance.

Lidocaine HCl (1%) blocked motor nerve conduction in control and diabetic rats ($P < 0.0001$) and exhibited a similar potency and time course in both groups (fig. 2). Procaine HCl (1%) blocked motor nerve conduction in control and diabetic rats ($P < 0.0001$) and produced a more complete block of motor nerve conduction in the diabetic group than in the control group ($P < 0.02$) (fig. 3).

In saline-treated animals, the proportion of extracellular space was not significantly different between control and diabetic nerves. Lidocaine induced edema in both groups, and this edema was significantly greater in diabetic nerves ($P < 0.05$; fig. 4). Whereas 2% lidocaine induced a similar absolute increase in extracellular space in both groups, the increase with 4% lidocaine was greater in the

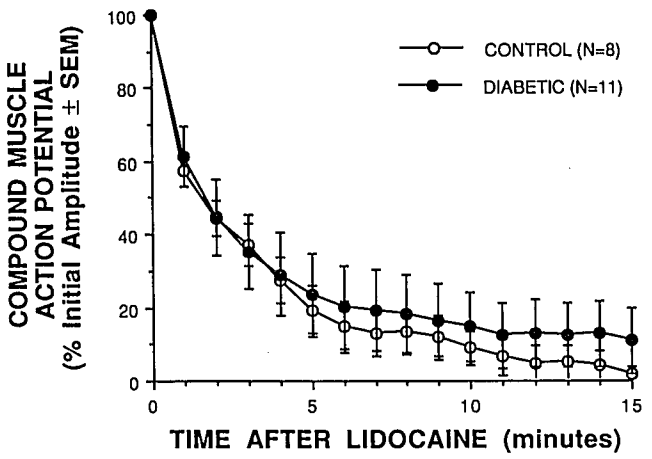

FIG. 2. Time course of motor conduction block with 1% lidocaine HCl in nerves of control and diabetic rats. Amplitudes of motor potentials were recorded once each minute after drug application next to the sciatic nerve. Data points are mean ± SEM for percent of initial amplitude at 0 min.

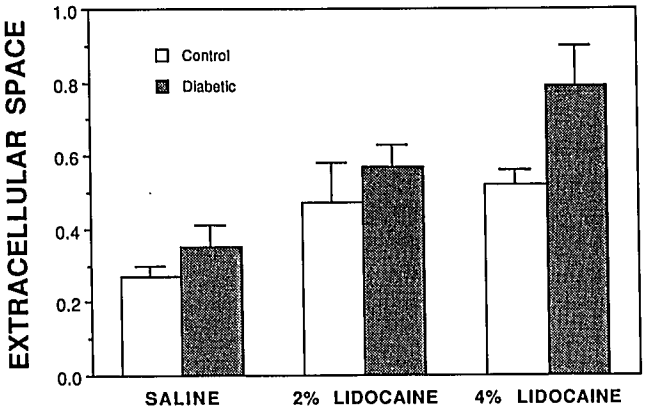

FIG. 4. Proportion of nerve occupied by extracellular space (+SEM) in control and diabetic nerves treated with 0.9% saline, 2% lidocaine HCl, or 4% lidocaine HCl 2 days previously. By two-factor analysis of variance, the increase in extracellular space, presumably corresponding to nerve edema, is greater overall in the diabetic than in the control groups ($P < 0.05$).

diabetic group (0.79 ± 0.11; mean ± SEM) than in the control group (0.52 ± 0.04) (unpaired t test, $P < 0.05$).

By light microscopy, nerve fiber injury scores (described in Materials and Methods) were greater in diabetic than in control nerves treated with lidocaine ($P < 0.05$, fig. 5). Severe nerve fiber injury (a score of 3 or 4) was observed only in the nerves of diabetic rats treated with 2% or 4% lidocaine. Light micrographs illustrating saline- and lidocaine-treated diabetic nerves are shown in figures 6 and 7. At a higher magnification, axonal degeneration and myelin sheath collapse secondary to axonal disintegration are evident (fig. 8).

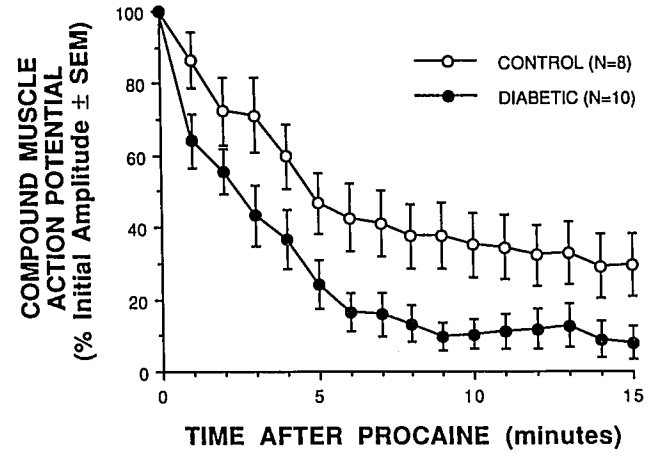

FIG. 3. Time course of motor conduction block with 1% procaine HCl in nerves of control and diabetic rats. Amplitudes of motor potentials were recorded once each minute after drug application next to the sciatic nerve. Data points are mean ± SEM for percent of initial amplitude at 0 min. Up to 15 min, the reduction of the motor response amplitude was greater in diabetic than in control nerves ($P < 0.05$); error bars did not overlap at any time point beginning 1 min after procaine administration.

Discussion

The streptozotocin-diabetic rat is the most widely studied model of experimental diabetes. Streptozotocin is a highly specific toxin that produces insulin-deficient diabetes by selective damage to the β cells of the islets of Langerhans.[17] In the current study, streptozotocin-injected rats exhibited elevated blood glucose levels, lower final body weight due to impaired maturation and muscle wasting, and reduced (although not significantly) MNCV. All of these disorders are characteristic of experimental diabetes[18] and are consequences of insulinopenia rather than direct effects of streptozotocin.

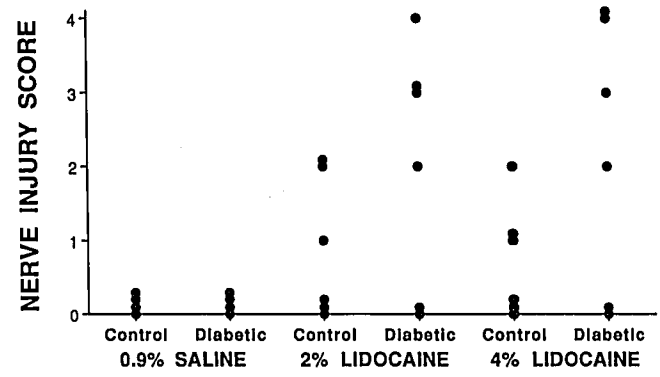

FIG. 5. Scores (0–4) for axonal degeneration or demyelination in control and diabetic nerves treated with 0.9% saline, 2% lidocaine HCl, or 4% lidocaine HCl 2 days previously. By nonparametric two-factor analysis of variance (Kruskal-Wallis), the lidocaine-induced nerve injury in the diabetic groups is significantly greater than that in the control rats ($P < 0.05$).

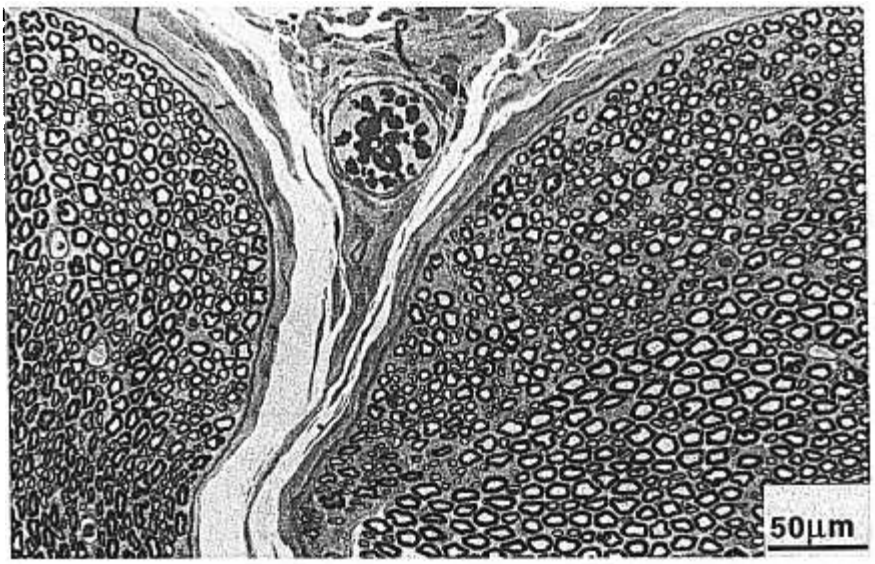

FIG. 6. Light micrograph depicting a normal-appearing diabetic rat nerve 2 days after extraneural administration of 0.9% NaCl. Scale bar = 50 μm.

Both lidocaine and procaine reduced motor compound action potential amplitude after injection adjacent to the sciatic nerve, indicating conduction block. Consistent with clinical experience, 1% lidocaine was more effective than 1% procaine in control nerves. However, the time course of procaine-induced conduction block was potentiated by diabetes sufficiently to be comparable to the block produced by lidocaine in control animals. Because the amplitude of the motor response in the control group may still be decreasing by 15 min (fig. 3), these data do not help to distinguish whether differences are due to pharmacodynamic or pharmacokinetic changes. No further potentiation was observed for lidocaine in nerves of diabetic rats. The cause of this selective potentiation of procaine's conduction block is unclear. Pharmacokinetic differences between these two drugs are more likely to favor potentiation of lidocaine rather than procaine.[19–21] It is therefore more likely that the more potent lidocaine was used in a dose that could not be further potentiated by diabetes. Dose–response studies are required to address this possibility.

High concentrations of local anesthetics can induce nerve edema and cause nerve injury.[9–11] In the current study, nerve injury was assessed after injections of saline or lidocaine, with the latter given at doses known to induce injury in normal nerves. Lidocaine was considered most suitable for our injury studies because its pharmacokinetic and physicochemical properties do not appear to be al-

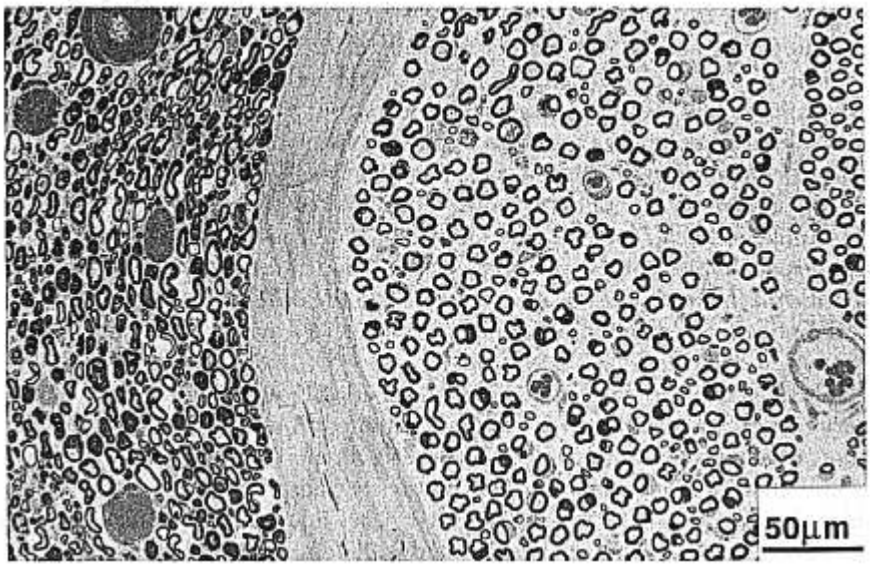

FIG. 7. Light micrograph depicting adjacent fascicles of a diabetic rat nerve 2 days after extraneural administration of 2% lidocaine HCl. The fascicle on the left is severely injured: virtually all nerve fibers are dystrophic or undergoing axonal degeneration. Nerve fibers of the larger, tibial fascicle, on the right, are widely separated by interstitial space, indicative of marked endoneurial edema, and nerve fiber pathology is much less evident than in the adjacent fascicle. Scale bar = 50 μm.

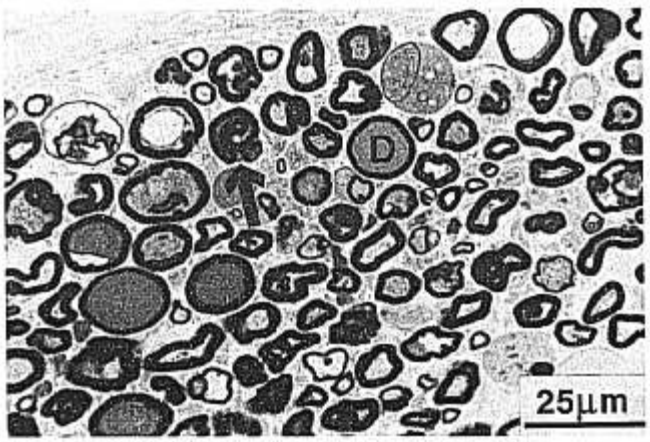

FIG. 8. Nerve fiber pathology in diabetic rat nerve 2 days after extraneural administration of 4% lidocaine HCl. In the field shown, several degenerating, darkly staining axons (an example is marked *D*) are illustrated. Eventually, degenerating axons will disintegrate, leaving a vacuous nerve fiber bounded by an apparently thin myelin sheath. Collapse of the myelin sheath occurs subsequent to complete axonal disintegration (*arrow*). Scale bar = 25 μm.

tered by diabetes (lidocaine-induced conduction block was similar in control and diabetic rats) and because lidocaine has wider clinical application than procaine.

In this study we used a morphometric assessment of endoneurial extracellular space to determine nerve edema. The extracellular space of diabetic nerves was slightly, but not significantly, increased after local injection of saline compared to control nerves. Although there has been a previous report of increased extracellular space in the nerve of streptozotocin-diabetic rats,[22] our current finding is consistent with many reports that, unlike other neuropathies,[23] streptozotocin diabetes is not associated with the development of substantial edema.[23,24] As previously reported,[10,11] local anesthetics induced a marked edema in control nerves. However, local injection of lidocaine was associated with greater edema in diabetic rats compared to controls. Enhanced local anesthetic–induced edema in nerves of diabetic rats is also in contrast to reports that diabetic nerve water accumulation is *less* than that of control nerves after galactose feeding[24] or Wallerian degeneration.[25] Our current findings suggest that it is unlikely that streptozotocin-induced diabetes causes a nonspecific prevention of water accumulation. More specific mechanisms must be sought to explain the differential effects of edema-inducing agents on nerve water content in diabetes.

The mechanisms by which local anesthetics induce nerve injury and edema remain to be determined. A proposed mechanism is that nerve edema causes an increase in endoneurial fluid pressure, which constricts transperineurial vessels and thereby causes ischemic nerve injury.[26] However, nerve fiber injury is correlated with *acute* (4 h) local anesthetic–induced decreases in blood flow[12] before the maximal accumulation of endoneurial edema by 48 h.[23] Thus, although local anesthetic–induced nerve injury is associated with nerve edema, injury appears to follow from the initial direct effects of local anesthetics on nerve blood supply. Furthermore, as illustrated in figure 7, a single nerve can have an edematous fascicle with minimal fiber injury adjacent to a smaller fascicle that is severely necrotic with little or no edema. It is noteworthy that toxic effects of the local anesthetic were apparent in all vessels of the small fascicles and the epineurium, but apparently patent vessels persisted in the large fascicle. Additional mechanistic studies are needed to resolve the edema- and injury-producing effects of local anesthetics.

The current observation that lidocaine-induced nerve injury was greater in diabetic rats than in control rats is in accord with evidence that local anesthetics produce injury by an ischemic mechanism[12] and that diabetic neuropathy is associated with decreased nerve blood flow.[6,7] Thus, if nerve blood flow is decreased by microangiopathy or changes in blood rheology, and the nerve is hypoxic, as has been reported in the sural nerve of diabetic patients,[27] then a nerve already compromised might be at increased risk for local anesthetic–induced ischemic nerve injury. Diabetic rats have been reported to be more susceptible to ischemic injury,[28,29] an effect that may be a consequence of hyperglycemia, as reported in humans.[30] This increased risk for ischemic injury appears to be inconsistent with reports that nerves of diabetic rats are resistant to hypoxic conduction blockade,[31] although resistance to hypoxic conduction block is an acute phenomenon and may not be relevant to maintenance of fiber structure after prolonged ischemic hypoxia. A shift to anaerobic glycolysis, as an adaptive response to chronic hypoxia due to reduced nerve blood flow,[16] could both be the mechanism of increased resistance to acute hypoxia and provide the potential for acidosis and therefore ischemic injury.[32] It will therefore be of interest to determine whether treatments known to prevent reduced nerve blood flow in diabetic rats[6,7] can also prevent the increase in fiber injury induced by local anesthetics in diabetic animals.

In summary, these experiments demonstrate enhanced conduction block with 1% procaine HCl, but not 1% lidocaine HCl, in nerves from diabetic rats. Although the anesthetic efficacy of lidocaine was unchanged, lidocaine-induced nerve edema and fiber injury both were greater in diabetic rats. These findings support the suggestions that diabetic patients may require less local anesthetic to produce anesthesia and that a reduction in dose may be necessary to prevent nerve injury by doses considered safe in nondiabetic patients. It remains to be determined whether these empiric findings in animal models have a clinical parallel.

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