Effects of Chronic α-Adrenergic Receptor Blockade on Peripheral Nerve Conduction, Hypoxic Resistance, Polyols, Na^+-K^+-ATPase Activity, and Vascular Supply in STZ-D Rats

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The effects of α-receptor blockade on nerve conduction, hypoxic resistance, ouabain-sensitive Na^+-K^+-ATPase, nerve polyols, and capillary density were examined in streptozocin-induced diabetic (STZ-D) rats. Nondiabetic and untreated diabetic control groups were used. Diabetes duration was 2 mo. There were two treated diabetic groups. A "prevention" group received 5 mg/kg prazosin for 2 mo from the induction of diabetes. A "reversal" group was untreated for the 1st mo and was given prazosin for the subsequent month. Conduction was measured in motor nerves supplying tibialis anterior and gastrocnemius muscles and sensory saphenous nerve. Diabetes resulted in 15–29% reductions in conduction velocity ($P < 0.01$). In the prevention group, conduction deficits were minimal compared with untreated diabetes ($P < 0.01$). In the reversal group, motor conduction was also substantially improved, although sensory conduction was not significantly affected. In vitro measurement of sciatic nerve hypoxic resistance revealed a 49% increase in the time taken for compound action potential amplitude to reach half its initial value with diabetes ($P < 0.01$). This was largely prevented by prazosin treatment ($P < 0.01$), although treatment had a lesser effect in the reversal group. Treatment had no effect on nerve polyol levels or Na^+-K^+-ATPase activity. Functional improvements with prazosin were probably based on increased vasa nervorum perfusion. There was a 20% elevation of endoneurial capillary density ($P < 0.01$) in both prevention and reversal groups. We conclude that vascular factors play an important role in the etiology of experimental diabetic neuropathy, and functional changes may be corrected by chronic vasodilator treatment. *Diabetes* 40:1652–58, 1991

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Putative explanations for the mechanisms underlying the early reduction in nerve conduction velocity (CV) and increased resistance to ischemic conduction failure (RICF) in diabetic patients and animal models have arisen from hypotheses based on metabolic or vascular factors (1). The metabolic view considers that functional changes depend on a *myo*-inositol deficit in nerves, with a consequent reduction in phosphoinositide turnover leading to reduced Na^+-K^+-ATPase activity. Therefore, metabolic demand is lowered, with RICF as one consequence. Fibers may become Na^+ loaded, causing Na^+-channel inactivation and reduced CV (2). The initial metabolic lesion has been linked with polyol-pathway activity because some of the changes may be prevented by aldose reductase inhibitors (ARIs) (3,4).

These metabolic abnormalities occur in energy-dependent processes and could therefore be influenced by changes in endoneurial perfusion resulting from vascular dysfunction (5). There is a reduction in nerve blood flow in diabetic rats causing endoneurial hypoxia (5), which has also been demonstrated in neuropathic patients (6). The underlying rheological changes and vasa nervorum microangiopathy produce an ATP supply deficit and increased dependence on anaerobic metabolism in diabetic animals (1), leading to reduced CV and increased RICF. Similar functional changes have been noted in nondiabetic rats and patients with chronic hypoxia (7,8).

We have previously found that chronic electrical nerve stimulation leads to improvements in CV (9). One possible mechanism is that increased metabolic activity promotes chronic vasodilation of vasa nervorum, leading to long-term improvements in vascular dynamics and a reduction in endoneurial hypoxia. This interpretation suggests that it may be possible to compensate for vasa nervorum insufficiencies in experimental diabetes by chronic vasodilator treatment.

Peripheral nerve vascular resistance is under strong sympathetic noradrenergic control, mediated by α-receptors (10). Adrenergic sympathectomy with guanethidine leads to increased sciatic nerve blood flow in rats (11,12). In this study, we examined the effect of long-term α-receptor blockade by prazosin on nerve CV, resistance to hypoxia, Na^+-K^+-ATPase activity, and polyol-pathway metabolites.

Chronic vasodilator treatment leads to increases in capillary density in skeletal muscles and heart (13,14). Capillary growth is readily stimulated in sciatic nerves from diabetic rats by treatment with essential fatty acids, although the mechanism is unknown (15). Vasodilator treatment could also encourage vasa nervorum angiogenesis, which would be expected to contribute to improved endoneurial perfusion. Therefore, we also measured sciatic nerve capillary density.

RESEARCH DESIGN AND METHODS

Male Sprague-Dawley rats (Aberdeen Univ. Breeding Colony), 19 wk old at the start of the study, were used. One group of nondiabetic rats were onset controls. Another group was given 5 $mg \cdot kg^{-1} \cdot day^{-1}$ p.o. prazosin (Sigma, Poole, UK) for 2 mo. Others were given 45 mg/kg i.p. streptozocin (STZ) in 20 mM sodium citrate buffer (pH 4.5). Diabetes was verified 24 h later by estimating hyperglycemia and glycosuria (Visidex II and Diastix; Ames, Slough, UK). Samples for plasma glucose measurement were taken on the day of final experiments.

Diabetic rats were divided into four groups. One was untreated for 2 mo, another for 1 mo. A "prevention" group was treated for 2 mo with 5 $mg \cdot kg^{-1} \cdot day^{-1}$ p.o. prazosin. A "reversal" group was untreated for the 1st mo and then given prazosin for the next month.

In final experiments (1–1.5 g/kg i.p. urethan anesthesia), CV was measured in vivo between sciatic notch and knee for motor branches supplying tibialis anterior (peroneal division) and gastrocnemius (tibial division) muscles. Sensory CV was measured in the saphenous nerve between groin and ankle. Methods have been previously described in detail (3,15).

RICF was measured in vitro (15). The contralateral sciatic trunk was removed and mounted on bipolar stimulating (proximal end) and recording (distal end) electrodes in a Plexiglas tissue chamber at 35°C. The chamber contained Krebs-Ringer solution (144 mM Na^+, 5 mM K^+, 2.5 mM Ca^{2+}, 1.1 mM Mg^{2+}, 25 mM HCO_3^-, 1.1 mM PO_4^{2-}, 1.1 mM SO_4^{2-}) with 5.5 mM glucose for nerves from nondiabetic rats and 40 mM glucose for the diabetic groups. Previous experiments have shown that varying glucose concentration between 5.5 and 40 mM does not have a significant effect on nerve hypoxic resistance under these conditions (unpublished observations). Bathing fluid was gassed with 95% O_2/5% CO_2 (pH 7.35). Nerves were equilibrated for 30 min, then the chamber was refilled with mineral oil pregassed with 100% N_2 for 1 h. Nerves were stimulated with just supramaximal pulses (1 Hz, 0.05-ms width, 10 mA), and compound action potential amplitude was monitored at 2-min intervals until it fell below 10% of its initial value.

The sciatic nerve trunk, between sciatic notch and its bifurcation at the knee, was removed and divided into five pieces of equal length, which were mounted together, along with skeletal muscle acting as support tissue. Samples were frozen in isopentane prechilled in liquid N_2. Ten-micrometer sections were cut on a cryostat, and capillary endothelium was stained for alkaline phosphatase with the method of Ziada et al. (14). Three sections, each 90 μm apart, were taken, and all capillaries in all fascicles were counted with the aid of a projection microscope. Fascicle outlines were traced and their areas measured with a digitizing pad linked to a microcomputer to calculate capillary density.

Separate groups of onset control, diabetic, and prazosin-treated diabetic rats were used for biochemical measurements in a parallel prevention study. Rats were anesthetized with 5% halothane in air, and both sciatic nerves were rapidly removed. Segments of nerve were frozen in liquid N_2 and stored at −80°C for subsequent analysis of sugar and polyol content or homogenized for determination of Na^+-K^+-ATPase activity.

Na^+-K^+-ATPase activity was estimated by a previously described method (16,17). One-centimeter segments taken from a standard site in the sciatic trunk proximal to its bifurcation at the knee were homogenized in 1 ml ice-cold 0.02 M Tris-HCl buffer (pH 7.6 at 25°C). Homogenates were centrifuged at 180 × *g* for 5 min at 4°C, and the supernatant was used for ATPase and protein determinations. ATPase activity was measured at 37°C with a reaction in which ATP hydrolysis was coupled to NADH oxidation, the latter being monitored at 340 nm in a spectrophotometer. Reaction mixtures were preincubated for 20 min before monitoring the linear fall in absorbance over a further 10 min. The incubation medium contained 130 mM NaCl, 30 mM KCl, 20 mM Tris Cl, 3 mM $MgCl_2$, 3 mM ATP, 1 mM phosphoenolpyruvate, 0.3 mM NADH, 45 μg/ml pyruvate kinase, and 24 μg/ml lactate dehydrogenase (Sigma). Ouabain-inhibited ATPase activity was estimated in the presence of 5 mM ouabain. Homogenate protein content was determined by a standard test kit (Bio-Rad, Hemel Hempstead, UK).

Sciatic nerve sugars and polyols were determined by gas chromatography of trimethylsilyl derivatives prepared from aqueous deproteinized extracts (18,19).

Data are expressed as means ± SE. One-way analysis of variance was performed, followed by Duncan's multiple-range test (20,21) to assign differences to individual groups when significance ($P < 0.05$) was attained.

RESULTS

Table 1 gives plasma glucose levels and body weights for the groups. Glucose was elevated five- to sixfold by diabetes and was unaffected by prazosin. There was an average body weight loss of 22% after 2 mo of diabetes regardless of treatment.

CV data are given in Table 2. For motor nerves, CV declined by 21 and 25% on average with diabetes duration of 1 and 2 mo, respectively. Preventive treatment with prazosin limited the decline to 5% (NS). In the reversal group, there was a similar marked improvement

TABLE 1
Plasma glucose and body weights for groups in the function study

	Plasma glucose (mM)	Body weight (g)	
		Start	End
Nondiabetic			
Onset	5.4 ± 0.3	471 ± 14	
2 mo + prazosin	6.5 ± 0.8	475 ± 14	567 ± 14
Diabetic			
1 mo	32.6 ± 3.1	502 ± 11	431 ± 16
2 mo	35.1 ± 1.9	546 ± 11	421 ± 21
Prazosin			
Prevention	40.6 ± 2.4	528 ± 20	399 ± 23
Reversal	35.9 ± 2.2	454 ± 10	376 ± 15

Values are means ± SE.

compared with untreated diabetes. Sensory saphenous CV was reduced 12% with 2 mo of diabetes. This was completely prevented by prazosin treatment. However, treatment was not successful in the reversal group ($P <$ 0.01 prevention vs. reversal). There were no significant CV differences between onset-control and prazosin-treated nondiabetic rats.

Data for hypoxic resistance measured in vitro are plotted in Fig. 1 for nondiabetic, 2-mo diabetic, and prevention and reversal prazosin-treated groups. After an initial period of hyperexcitability (22) when compound action potential amplitude increased, compound action potential amplitude declined more rapidly in nondiabetic and prazosin-treated nerves than diabetic control nerves. The decline was more apparent with preventive than reversal prazosin treatment. This may be seen for times taken for compound action potential amplitude to be reduced by 50 and 80% (T_{50} and T_{80}; Table 2). These were increased 48 and 51%, respectively, for 2 mo of diabetes. With preventive prazosin treatment, levels comparable with those of 1-mo untreated diabetes were found. Thus, treatment slowed the progression of hypoxic resistance by ~50%. Reversal was less successful, with 32 and 36% increases in T_{50} and T_{80} compared with

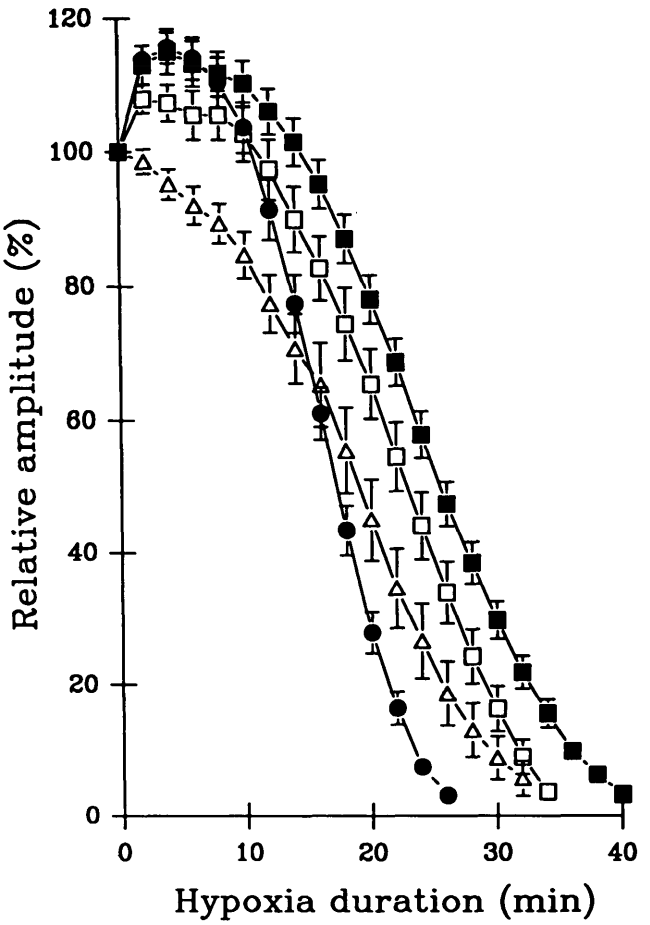

FIG. 1. Changes in relative amplitude of sciatic nerve compound action potential in vitro with duration of hypoxia. ●, Nondiabetic control; ■, 2-mo diabetic control; △, prazosin prevention diabetic; □, prazosin reversal diabetic. Values are means ± SE.

nondiabetic controls. These values are midway between 1- and 2-mo untreated diabetic groups—significantly worse than the former ($P < 0.05$) but improved compared with the latter ($P < 0.05$). Therefore, reversal treatment apparently did not correct the deficit due to the initial

TABLE 2
Conduction velocity in sciatic motor nerves supplying tibialis anterior and gastrocnemius muscles, sensory conduction velocity in saphenous nerve, and hypoxic resistance of sciatic trunk

		Conduction velocity (m/s)				Hypoxic resistance (min)	
	n	TA	G	Av	S	T_{50}	T_{80}
Nondiabetic							
Onset	20	65.1 ± 1.9	65.4 ± 1.9	65.3 ± 1.4	59.3 ± 1.3	17.3 ± 0.5	21.2 ± 0.5
2 mo + prazosin	10	66.4 ± 1.7	67.4 ± 1.4	66.9 ± 1.4	60.4 ± 1.2	17.0 ± 1.1	21.0 ± 1.3
Diabetic							
1 mo	10	50.2 ± 2.2*	52.4 ± 1.8*	51.3 ± 1.7*	50.7 ± 1.0*	19.5 ± 0.9†	24.8 ± 0.9*
2 mo	20	47.7 ± 1.3*	50.7 ± 1.3*	49.2 ± 1.0*	52.1 ± 1.2*	25.5 ± 0.7*	31.9 ± 0.8*
Prazosin							
Prevention	12	59.0 ± 2.2‡	64.7 ± 1.8‡	61.8 ± 1.7‡	61.1 ± 1.4‡	19.1 ± 1.3‡	24.9 ± 1.6†‡
Reversal	12	59.3 ± 1.6‡§	62.1 ± 1.9‡§	60.7 ± 1.6‡‖	53.8 ± 1.4*	22.8 ± 0.9*§¶	28.7 ± 0.9*§¶

Values are means ± SE. TA, tibialis anterior; G, gastrocnemius; Av, average motor conduction for TA and G; S, saphenous; T_{50}, time for 50% compound action potential reduction; T_{80}, time for 80% compound action potential reduction.
*$P < 0.01$, †$P < 0.05$, vs. nondiabetic onset.
‡$P < 0.01$, ¶$P < 0.05$, vs. 2-mo diabetic.
§$P < 0.05$, ‖$P < 0.01$, vs. 1-mo diabetic.

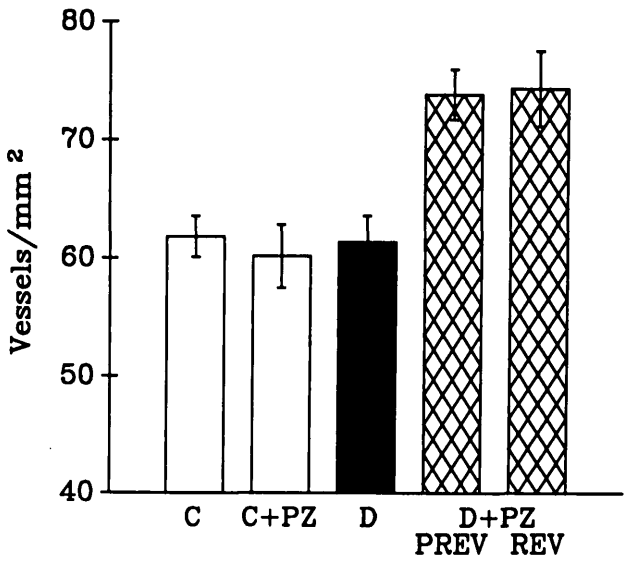

FIG. 2. Sciatic nerve endoneurial capillary density. *Open bars*, nondiabetic control groups (C, untreated; C + PZ, prazosin-treated); *solid bar*, 2-mo diabetic (D) control; *crosshatched bars*, prazosin-treated diabetic (D+PZ; prev, 2-mo prevention group; rev, reversal group with treatment for 2nd mo of diabetes). Values are means ± SE.

month of untreated diabetes, although it slowed the development of further increases in hypoxic resistance. Prazosin did not have any significant effect in nondiabetic rats.

Data for endoneurial capillary density from sciatic trunk are shown in Fig. 2. The nondiabetic control group had a mean density of 61.8 ± 1.7 vessels/mm^2. This was not significantly affected by prazosin treatment. Diabetes alone also had little effect on capillarization. However, in the prazosin-treated prevention and reversal groups, capillary density was increased by ~20% compared with diabetic or nondiabetic control groups ($P < 0.01$).

Separate diabetic and nondiabetic control and prevention prazosin-treated groups provided fresh samples for measurement of sciatic nerve polyols and ouabain-sensitive Na^+-K^+-ATPase activity. Plasma glucose levels were 31.6 ± 1.4 mM for untreated diabetes and 32.7 ± 1.5 mM with prazosin treatment. Corresponding values for starting and end-point body weights were 491 ± 14 and 372 ± 7 g for untreated diabetes and 521 ± 12 and 428 ± 8 g with prazosin treatment. Values are in reasonable agreement with those for groups used for functional measurements (Table 1). Data on sciatic nerve polyols and Na^+-K^+-ATPase activity are given in Table 3. Nerve sorbitol and fructose were increased 9.6- and 10.2-fold with diabetes. This was not affected by prazosin treatment. *myo*-Inositol levels were reduced 61% with diabetes, and there appeared to be a trend toward improvement with prazosin, although this was not statistically significant. Ouabain-sensitive Na^+-K^+-ATPase activity was reduced 61% by diabetes and was not significantly altered by prazosin.

DISCUSSION

The data demonstrate that treatment with prazosin, an α-adrenoreceptor blocker with greatest α_1 affinity, prevented or partially reversed the effects of STZ-D on nerve CV. It also decreased the rate of development of hypoxic resistance. The underlying mechanism probably depends on a blockade of sympathetic vasoconstrictor tone in vasa nervorum, leading to reduced vascular resistance, elevated blood flow, and a consequent reduction in endoneurial hypoxia. We have previously shown that guanethidine-induced adrenergic nerve degeneration results in endoneurial blood flow and motor CV improvements (12). Prazosin would be expected to have similar functional effects without damaging the sympathetic supply and would also block the α_1-mediated activity of circulating catecholamines. This is an important action because reactivity to norepinephrine, particularly for smaller resistance vessels, is enhanced in diabetic rats (23). This study is the first to report adrenergic vasodilator effects on the prevention of sensory CV deficits and the development of hypoxic resistance. Together with other investigations with different treatments that increase nerve perfusion, such as chronic electrical stimulation (9) and vasodilator prostaglandin E_1 analogues (24), the data strongly support the view that a major factor in the development of CV and RICF abnormalities in diabetes is the reduction in endoneurial blood flow, which produces a hypoxic microenvironment for axons and Schwann cells (1).

Prazosin's effects on sciatic motor CV were equal in prevention and reversal groups. However, only prevention was successful for sensory saphenous fibers. The reason for this difference is not clear. It may relate to differences in vascular beds between the two nerves, saphenous perhaps having a sparser blood supply or reduced noradrenergic innervation. No information is yet

TABLE 3
Sciatic polyols and ouabain-sensitive Na^+-K^+-ATPase activity in nerves from control rats, from 2-mo untreated diabetic rats, and from 2-mo diabetic rats given preventive prazosin treatment

	Sciatic polyols (μg/g wet wt)			Ouabain-sensitive Na^+-K^+-ATPase (μmol ATP · h^{-1} · mg^{-1} protein)
	Sorbitol	Fructose	*myo*-Inositol	
Control	28 ± 2	82 ± 7	527 ± 34	5.56 ± 0.76
Diabetic				
2 mo	269 ± 36*	833 ± 49*	204 ± 10*	2.15 ± 0.28*
Prazosin prevention	266 ± 25*	864 ± 82*	271 ± 15*	2.27 ± 0.40*

Values are means ± SE for 10 rats/group.
*$P < 0.01$ vs. control.

available on this point. Saphenous CV is very sensitive to diabetes in that it declines rapidly after induction. However, this is not irreversible because 2 mo of ARI treatment corrected the deficit from 2-mo untreated diabetes (4). It is possible that saphenous CV changes may prove reversible with more effective vasodilator treatment.

Increased sciatic RICF was partially prevented by treatment; however, reversal had less effect. The data are consistent with the interpretation that prazosin halved the rate of increase in RICF, which was progressive with diabetes, in both prevention and reversal groups. This may be contrasted with effects on motor CV where the prevention and reversal groups had similar values. Thus, CV and RICF may be dissociated to some degree, perhaps reflecting differences in underlying mechanisms. The cause of increased RICF is disputed. Lattimer et al. (2) considered that both RICF and CV deficits depend on reduced Na^+-K^+-ATPase activity. Low et al. (1) suggested that hypoxic resistance results as an adaptation to endoneurial hypoxia toward greater use of anaerobic metabolism, and the data are more consistent with this hypothesis. In the reversal group, increased blood flow would minimize hypoxia and therefore allow aerobic ATP production to correct CV deficits. However, initial exposure to hypoxia over the 1st mo of diabetes would enhance anaerobic metabolism. This could remain elevated after treatment; it is not deleterious, and there is no obvious adaptive stimulus to promote a swift return to near total reliance on aerobic energy metabolism, particularly given the glucose availability in diabetes. It is likely that some low-level hypoxia remained during treatment because RICF continued to increase, albeit at a much reduced rate.

The close relationship between vascular factors and nerve dysfunction can be seen in Fig. 3. The *top panel* is a scatterplot and linear regression of average sciatic CV against capillary density ($r = 0.61$, $P < 0.0001$) for treated and untreated diabetic rats. The *bottom panel* shows a negative correlation between T_{50} and capillarization ($r = 0.41$, $P = 0.0075$). It is likely that increased vascularization with prazosin contributed to improved perfusion and endoneurial oxygenation if the newly formed vessels were patent. However, it is possible that angiogenesis is not necessary for improved nerve function, the vasodilation by prazosin being sufficient. Aldose reductase inhibition improves sciatic nerve blood flow in diabetic rats (24); however, it does not cause angiogenesis (N.E.C., M.A.C., unpublished observations).

Capillary density did not increase in prazosin-treated nondiabetic rats. This is in agreement with the effects of guanethidine in nondiabetic rats. However, in those experiments, vascular changes did occur, because there was a 40% increase in vessel size (11). Although measurements were not made in this study, it is likely that prazosin would produce similar effects. The sequence of changes with chronic vasodilator treatment proceeds first via an increase in the proportion of vessels patent, second through increased vessel size, and last through angiogenesis (13). The stimulus for vessel growth varies in different vascular beds. In some (e.g., the lungs), relative hypoxia seems important, whereas in others

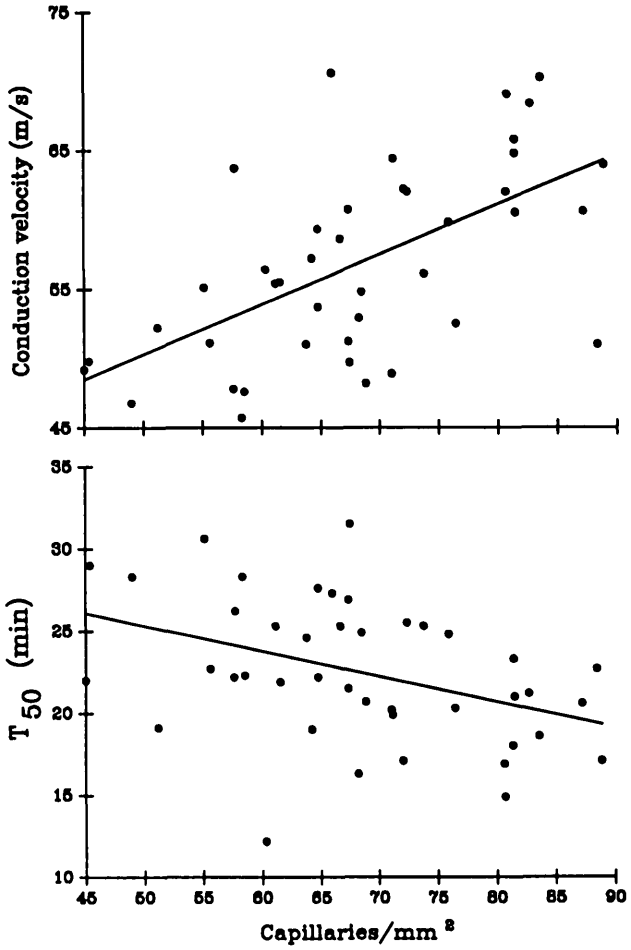

FIG. 3. Linear regression between sciatic nerve endoneurial capillary density and average motor conduction velocity or duration of hypoxia necessary to produce 50% conduction block (T_{50}) for prazosin-treated and age-matched diabetic rats. Best-fit linear regression equations were conduction velocity (m/s) = 31.6 + 0.373 × capillary density (vessels/mm^2) and T_{50} (min) = 32.9 − 0.153 × capillary density (vessels/mm^2).

(e.g., skeletal muscles), the main factor is the mechanical effect of increased blood flow and capillary pressure on endothelium (13,14). Clearly, hypoxia at the level found in diabetes (5) is not a sufficient stimulus for peripheral nerve. In these experiments, it is likely that angiogenesis depended on both increased mechanical stimulation of endothelium and the presence of relative hypoxia. This would explain why angiogenesis was only found with the combination of treatment and diabetes. An additional costimulus for vessel growth that cannot be ruled out could be increased levels of circulating proliferative factors. In previous work with essential fatty acid dietary supplementation, a similar increase in sciatic nerve capillarization was noted, although it was not clear whether there was direct prostanoid-dependent angiogenesis or whether the results were caused by increased blood flow due to vasodilation (15). The data in this study suggest that the latter provides a likely unifying explanation.

Prazosin treatment did not affect nerve sorbitol or fructose levels; therefore, it is unlikely that beneficial functional effects depended on a reduction of polyol-

pathway metabolites or activity. *myo*-Inositol levels were reduced by diabetes and were not significantly affected by treatment; thus, a general improvement in *myo*-inositol metabolism probably did not contribute. Although these data do not exclude normalization in a small discrete pool of nerve *myo*-inositol (2), a major functional effect is unlikely, because in our experimental model, dietary *myo*-inositol supplementation did not improve CV (4). The biochemical data are in line with those seen for some other treatments. Tomlinson et al. (25) demonstrated that essential fatty acid supplementation prevents CV deficits but does not affect sorbitol or *myo*-inositol levels.

The reduction in Na^+-K^+-ATPase with diabetes is in agreement with findings of others (2,16). However, this was unaffected by prazosin, although CV and RICF were markedly improved, suggesting that the ATPase deficit is not a primary cause of impaired function in diabetic nerves. This argument finds some support from the literature. In diabetic mice, CV is reduced without an Na^+-K^+-ATPase deficit (26,27), and in rats, ATPase activity is normal at a time CV deficits would be expected (4,16). In addition, although some workers have suggested that ARIs improve CV in diabetic nerves through a mechanism involving normalization of *myo*-inositol, phosphoinositide metabolism, and Na^+-K^+-ATPase (2), others have failed to find an effect of ARIs on Na^+-K^+-ATPase (16) despite CV improvements (3). Endoneurial hypoxia could theoretically cause the Na^+-K^+-ATPase deficit, because increased activation of phospholipases reduces phosphoinositide levels available for ATPase stimulation (28). However, the data for prazosin treatment suggest that this putative mechanism may not make an important contribution in practice.

Several studies have demonstrated CV (3,4) and RICF (29) improvements with ARIs. Given the lack of effect on nerve polyols in this study, which primarily resulted from aldose reductase activity in Schwann cells and axons (30), and the importance of vascular factors that the data emphasize, it is plausible that a key ARI action may be on endoneurial vessels. This would not be reflected by measurements of nerve metabolite levels because it would be masked by the much greater production by neural cells. Endothelium contains aldose reductase (31), and its function is impaired by diabetes. In the longer term, production of the local vasodilator prostacyclin is reduced (32), and vessel endothelium from diabetic animals shows very early hyperglycemia-dependent increases in vasoconstrictor thromboxane A_2/prostaglandin H_2 synthesis (33–35). ARIs have other endothelium-targeted effects: for example, preventing increased capillary permeability in diabetic and galactosemic rats (36,37). It is important to ascertain whether ARIs generally improve endothelial function, because they have been reported to increase sciatic nerve blood flow in diabetic rats (24).

In conclusion, chronic vasodilator treatment with prazosin prevented and partially reversed changes in nerve function in experimental diabetes. Growth of endoneurial vessels was also promoted. Given that endoneurial hypoxia is thought to play an important role in the etiology of neuropathy in patients (6), treatment with a suitable vasodilator may have therapeutic value.

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