Selective Effects of *Myo*-inositol Administration on Sciatic and Tibial Motor Nerve Conduction Parameters in the Streptozocin-Diabetic Rat

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SUMMARY

Time-dependent effects of experimental diabetes and dietary *myo*-inositol supplementation on motor nerve conduction velocity (MNCV) were assessed in two populations of motor nerve fibers in the rat hind limb. These two populations of large myelinated motor fibers, which innervate the musculature of the calf and the foot, were differentially affected by growth, experimental diabetes, and dietary *myo*-inositol. Dietary *myo*-inositol supplementation ameliorated the diabetes-induced MNCV impairment in both nerve fiber populations but with different time courses. These observations suggest metabolic or physiologic heterogeneity among populations of large myelinated motor fibers which may partially explain published discrepancies regarding the efficacy of dietary *myo*-inositol supplementation in improving slowed MNCV in the streptozocin-diabetic rat. DIABETES *31*:573–578, July 1982.

Metabolic abnormalities in peripheral nerve resulting from insulin deficiency and/or hyperglycemia are thought to contribute to the development of the common forms of diabetic polyneuropathy. The effects of hyperglycemia and/or insulin deficiency on peripheral nerve biochemistry, physiology, and structure have been extensively explored in the streptozocin(SZ)-diabetic rat model. We have proposed that alterations in peripheral nerve *myo*-inositol metabolism consequent to insulin deficiency and/or hyperglycemia in part mediate the impairment of nerve conduction in acute streptozocin diabetes.[1] This hypothesis was based on the following observations: (1) acute streptozocin diabetes in 150-g rats impairs sciatic motor nerve conduction velocity (MNCV) to the triceps surae muscle and reduces sciatic nerve *myo*-inositol content within 2 wk; (2) fastidious insulin treatment which eliminates hyperglycemia prevents the decline in both sciatic nerve *myo*-inositol and MNCV, while less rigorous insulin treatment fails to prevent either; and (3) dietary *myo*-inositol supplementation that pharmacologically elevates plasma *myo*-inositol concentration normalizes both sciatic MNCV and nerve *myo*-inositol content, despite persistent severe hyperglycemia and elevated nerve glucose, fructose, and sorbitol content.[2]

Decreased sciatic nerve *myo*-inositol content has been observed consistently in acute SZ-diabetic rats of various ages,[3,4] but recent studies in older SZ-diabetic rats[5,6] questioned the reduction of sciatic nerve *myo*-inositol content as well as the beneficial electrophysiologic effects of dietary *myo*-inositol supplementation. The present studies were undertaken to reexamine the role of altered *myo*-inositol metabolism in the impairment of nerve conduction in the SZ-diabetic rat. The effects of experimental diabetes and dietary *myo*-inositol supplementation on MNCV in the hind limb were assessed in different populations of motor fibers and at different anatomic levels, and were compared with regional nerve *myo*-inositol concentration at the same sites. These studies suggest that regional differences within the rat PNS, as well as variations in experimental design and animal model, contribute to these discrepant published observations, and we confirm the beneficial effect of dietary *myo*-inositol supplementation on MNCV in the acute SZ-diabetic rat.

METHODS

Animal models. Male Wistar rats, initial weight either 145–155 or 215–225 g, were fed ad libitum throughout the study period. Body weight was determined thrice weekly. The "standard" diet consisted of pellets composed of 18% vitamin-free casein, 68% sucrose, 10% vegetable oil, 4% inorganic salts, all known rat vitamin requirements, and 0.011% free *myo*-inositol by weight (Nutritional Biochemical

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Corporation, Cleveland, Ohio).[2] The "1% *myo*-inositol" diet was provided by the same supplier and was identical except that it contained 1% free *myo*-inositol. Experimental diabetes was induced by streptozocin (Upjohn Company, Kalamazoo, Michigan) injected in 0.10 ml of 0.01 M citrate buffer, pH 5.5, into the tail vein of rats fasted overnight. Because the diabetogenicity of streptozocin increases with the age of the rats, 65 mg/kg was used in the younger group of rats and 60 mg/kg in the older group of rats.[7] For inclusion in the study, diabetic rats had to have nonfasting plasma glucose concentrations exceeding 300 mg/dl at 24 and 48 h, and 14 and/or 28 days after injection.[2]

Nerve conduction studies. Animals were anesthetized with sodium pentobarbitol 30–40 mg/kg injected intraperitoneally and MNCV was measured by three methods. "Sciatic-posterior tibial" MNCV was measured as previously described.[8] Briefly, 0.1-ms square-wave stimuli were applied at the sciatic notch (S) and ankle (A), and the evoked muscle action potential recorded in the first interosseous muscle in the foot (f); hence the convention SA_f MNCV. "Sciatic" MNCV was measured by two methods. In both, 0.2-ms square-wave pulses were applied through teflon-coated stimulating electrodes with bare tips to the surgically exposed sciatic nerve at the sciatic notch (S) and popliteal fossa or "knee"(K). The resultant muscle action potential was recorded either in the triceps surae (t) (gastrocnemius plus soleus muscles) as previously reported[2] or in the first interosseous muscle in the foot (f). Hence the conventions SK_f and SK_t. SK_f and SK_t measured conduction occuring via different fiber populations within the same segment of sciatic nerve, while SK_f and SA_f measured conduction through different lengths of the same fiber population. In all three methods, core temperature was maintained at 37°C by a thermistor-controlled infrared lamp feedback apparatus. Stimulus intensity was limited to the smallest voltage that consistently produced maximal muscle response. Evoked muscle action potential was recorded at the stated locations using uninsulated subcutaneous electrodes, and displayed and photographed on an oscilloscope. The distance between the stimulating electrodes, measured by calipers, was divided by the difference between the proximal and distal latencies. Each was measured from the stimulus artifact to the onset of the evoked muscle action potential, to calculate MNCV over the intervening nerve segment. The surgically exposed sciatic nerve was maintained at 35°C by an additional thermistor-controlled infrared lamp for SK_f and SK_t MNCV measurements.

Experimental design. MNCV was measured in three groups of normal, diabetic, and diabetic rats fed 1% *myo*-inositol diets using several experimental paradigms. In group I (starting weight 150 g), "sciatic-posterior tibial" conduction (SA_f MNCV) was measured before induction of diabetes and 2 and 4 wk later in normal and SZ-diabetic rats that were maintained on the standard or 1% *myo*-inositol diets. Sequential studies were possible because of the noninvasive nature of the techniques and were dictated by the expected age-related increases in normal MNCV. In group II (starting weight 150 g), conduction velocity in the sciatic portion of these same fibers was assessed by measuring SK_f MNCV 2 wk after induction of diabetes. In both groups I and II, the *myo*-inositol-supplemented diabetic rats received the 1% *myo*-inositol diet from the establishment of the diabetic state, i.e., 48 h after streptozocin administration. In group III (starting weight 225 g), larger rats were used to facilitate isolation of the posterior tibial nerve for biochemical study. *Myo*-inositol supplementation was delayed until day 7, since normalization of plasma glucose for days 7–14 by insulin treatment previously preserved normal SK_t MNCV.[2] Both SK_t MNCV and SA_f MNCV and tibial and sciatic nerve *myo*-inositol content were measured in group III at day 14 to compare the biochemical and physiologic effect of short-term *myo*-inositol supplementation in experimental diabetes. Proximal segments of the motor fibers to the foot muscles occupy the same fascicle as the sciatic nerve fibers to the triceps surae, but their distal portions extend into and traverse the posterior tibial nerve. Therefore, local environmental factors within the tibial nerve might influence conduction over their entire length (SA_f) including the proximal portion (SK_f) within the sciatic nerve fascicle.

Analytic techniques. Tissue samples for biochemical analysis were routinely obtained from the nerve contralateral to the one studied electrically or bilaterally in animals in whom MNCV was not assessed. Sciatic nerve segments from the midthigh region and tibial nerve segments from the midcalf region were routinely selected since they proved to be relatively free of extraneural connective tissue contamination. The nerve segments for biochemical analysis were rapidly removed, cleaned of adherent blood and connective tissue, and frozen in liquid nitrogen. Blood was collected by cardiac puncture, chilled, and then centrifuged at 3000 × *g* for 15 min at 4°C; the resulting plasma was rapidly frozen. Free *myo*-inositol was determined in protein-free Somogyi filtrates of plasma or nerve homogenates as previously described, and expressed per ml of plasma or per g wet weight of whole nerve.[2] The determinations of *myo*-inositol were performed on trimethylsilyl derivatives of lyophilized aliquots of the plasma or nerve filtrates containing α-D-methyl mannopyranoside as an internal standard in a Varian 3700 gas-liquid chromatograph on a 6-ft × 4 mm 3% SE-30 Gaschrom Q glass column at 185°C with a nitrogen carrier-gas flow rate of 40 ml/min using a flame ionization detector maintained at 250°C. Standard curves were determined daily, and the recovery of added *myo*-inositol to nerve or plasma samples consistently exceeded 95%. Plasma glucose was determined in tail-vein blood collected in heparinized 40-μl capillary tubes and centrifuged in a microhematocrit centrifuge; 0.01 ml of plasma was withdrawn and injected into a previously standardized Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, California). Plasma glucose concentration when rats were killed was determined in heparinized blood obtained by cardiac puncture.[2] Results are expressed as mean ± standard error of the mean and significance of differences was calculated by the Student's two-tailed *t* test.[10] Sequential MNCV determinations in group I were treated as paired samples and analyzed by the Student's *t* test for paired differences.[10]

RESULTS

Group I (Table 1). Streptozocin administration in group I rats produced severe persistent hyperglycemia and blunted weight gain but had no effect on plasma *myo*-inositol in rats fed the standard diet as previously reported.[2] The 1% *myo*-inositol diet raised plasma *myo*-inositol 10-fold but did not alter plasma glucose or weight gain in the diabetic rat. Ini-

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TABLE 1
Effect of acute SZ diabetes and dietary *myo*-inositol (MI) supplementation on sciatic-posterior tibial MNCV to the foot muscles (SA_f) in 150-g rats (group I)

Animal diet (N)	Plasma concentration		Sciatic-tibial SA_f MNCV (m/s)			ΔSciatic-tibial SA_f MNCV (m/s)			Body weight (g)		
	Glucose (mg/dl)	MI (μM)	Initial	2 wk	4 wk	0–2 wk	2–4 wk	0–4 wk	Initial	2 wk	4 wk
Normal STD (12)	193 ± 10	32 ± 3	31.0 ± 0.6	37.9 ± 0.9	41.9 ± 1.1	+ 6.9 ± 0.9	+ 4.0 ± 1.2	+10.9 ± 0.7	151 ± 2	245 ± 8	297 ± 15
				< 0.025	< 0.005	< 0.025		< 0.001		< 0.001	< 0.001
Diabetic STD (8)	669 ± 42	27 ± 2	30.9 ± 0.9	35.0 ± 0.7	37.1 ± 0.9	+ 4.1 ± 0.4	+ 2.1 ± 0.7	+ 6.2 ± 0.7	146 ± 4	172 ± 8	180 ± 13
				NS	< 0.005	NS	<0.005	< 0.05		NS	NS
Diabetic 1% (8)	708 ± 23	276 ± 29	31.0 ± 0.7	33.8 ± 0.6	40.7 ± 0.8	+ 2.9 ± 0.7	+6.8 ± 1.2	+9.7 ± 1.4	152 ± 3	197 ± 10	217 ± 18
											< 0.005

Plasma glucose and *myo*-inositol values were determined at the completion of the experiment. Values are expressed as mean ± SEM, figures in parentheses refer to number of animals in each group, and bracketed figures refer to P values of differences between groups computed by the Student's *t* test. MI = plasma *myo*-inositol concentration. STD = standard diet. 1% = 1% *myo*-inositol diet.

tial sciatic-posterior tibial (SA_f) MNCV was similar in the age-matched normal and diabetic groups. Although a significant increase in SA_f MNCV was noted for the three groups during each consecutive 2-wk interval, the increase (Δ) in MNCV at 2 and 4 wk was reduced in the diabetic group fed the standard diet compared with the normal controls. The diabetics fed 1% *myo*-inositol also had a similarly significant reduction in SA_f MNCV at 2 wk compared with the normal controls, but at 4 wk the SA_f MNCV had increased to normal values significantly different from the diabetics on the standard diet. This difference resulted from a significantly greater Δ MNCV in the *myo*-inositol supplemented animals over the second 2 wk of the study. No such effect from dietary *myo*-inositol supplementation was evident during the first 2 wk of the study. Thus, *myo*-inositol supplementation reversed rather than prevented the SA_f MNCV impairment in the SZ-diabetic rat, but this effect was delayed despite constant dietary *myo*-inositol supplementation begun with the onset of diabetes.

Group II (Table 2). In contrast to the delayed effect of *myo*-inositol supplementation on SA_f MNCV, dietary *myo*-inositol supplementation had been shown to prevent impairment in sciatic motor conduction to the triceps surae muscles (SK_t MNCV) in 2-wk SZ-diabetic rats.[2] We therefore assessed the effects of dietary *myo*-inositol and experimental diabetes on sciatic motor conduction in adjacent motor fibers to the interosseous foot muscles (SK_f MNCV). These fibers, identical to the ones assessed by SA_f MNCV, in their sciatic portion occupy the same fascicle and are in close proximity with the motor fibers to the triceps surae muscles.

Two-week SZ diabetes and dietary *myo*-inositol supplementation had the expected effects on plasma glucose and *myo*-inositol concentrations in group II rats (Table 2). SK_f MNCV was significantly impaired in diabetic rats fed either the standard or the 1% *myo*-inositol diet; *myo*-inositol supplementation had no discernible effect on SK_f MNCV in the 2-wk diabetic animals. In contrast, the conduction impairment resulting from 2-wk experimental diabetes in the normally faster-conducting fibers to the triceps surae muscles was prevented by dietary *myo*-inositol supplementation. Thus, 2-wk dietary *myo*-inositol supplementation increased diabetic MNCV in nerve fibers to the triceps surae but not in adjacent portions of motor fibers to the intrinsic foot muscles. Different subgroups of myelinated motor nerve fiber segments within the same fascicle and equidistant from the anterior horn cells responded differentially to *myo*-inositol supplementation.

Group III (Table 3). A slightly reduced streptozocin dose[7] and 1% dietary *myo*-inositol supplementation produced the expected changes in plasma glucose and *myo*-inositol concentrations at 2-wk (Groups III-a). Sciatic MNCV to the triceps surae (SK_t MNCV) was similar to that previously reported in lighter and younger animals at 2 wk (compare this with Table 2). However, the 2-wk sciatic-posterior tibial (SA_f) MNCV was significantly faster in these normals than in the younger and lighter group I normal animals (42.6 ± 0.8 vs. 37.9 ± 0.9 M/s, $P < 0.001$, see Table 1), and was consistent with the age-related increase in sciatic-posterior tibial MNCV previously noted by others.[11,12] Both SA_f MNCV and SK_t MNCV in diabetic rats fed the standard diet were significantly impaired when compared with normal control values. The 1% *myo*-inositol diet normalized sciatic (SK_t) but had

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TABLE 2
Effect of 14-day SZ diabetes and dietary *myo*-inositol on sciatic MNCV in motor fibers to the foot muscles (SK_f MNCV) and the triceps surae (SK_t MNCV) (group II)

Animal diet (N)	Plasma glucose (mg/dl)	Plasma *myo*-inositol (μM)	Sciatic MNCV (m/s)	
			Fibers to foot muscles	Fibers to triceps surae[2]
Normal STD (10)	174 ± 11	30 ± 2	47.4 ± 2.2	64.6 ± 0.9 (20)
			< 0.05	<0.001
Diabetic STD (7)	747 ± 34	36 ± 6	40.7 ± 2.2	50.1± 0.9 (35)
			NS	<0.001
Diabetic 1% (7)	755 ± 27	198 ± 25	40.4 ± 2.3	58.0 ± 1.4 (19)

Conduction data in the fibers to the triceps surae were previously published and are included for comparison.[2] Numbers in parentheses refer to number of animals studied.

TABLE 3
Effect of 14-day SZ diabetes and dietary *myo*-inositol on sciatic-to-triceps (SK_t) and sciatic-posterior tibial (SA_f) MNCV in 225-g rats (group III-a)

Animal diet (N)	Plasma glucose (mg/dl)	Plasma *myo*-inositol (μM)	Sciatic-to-triceps MNCV (m/s)	Sciatic-tibial MNCV (m/s)
Normal STD (15)	186 ± 13	26 ± 3	61.9 ± 0.6	42.6 ± 0.8
			< 0.001	< 0.001
Diabetic STD (14)	670 ± 20	24 ± 1	51.0 ± 1.0	36.5 ± 0.5
			< 0.001	NS
Diabetic 1% (12)	611 ± 34	207 ± 30	60.5 ± 0.6	38.5 ± 1.1

SA_f MNCV was first measured in each animal, after which the contralateral sciatic nerve was exposed for assessment of SK_t MNCV.

TABLE 4
Effect of 14-day SZ diabetes and dietary *myo*-inositol on sciatic and tibial nerve *myo*-inositol in 225-g rats (group III-b)

Animal diet (N)	Plasma glucose (mg/dl)	Plasma *myo*-inositol (μM)	(N)	Sciatic *myo*-inositol (mmol/kg)	Tibial *myo*-inositol (mmol/kg)
Normal STD (6)	199 ± 15	30 ± 3	(12)	2.76 ± 0.06	3.63 ± 0.25
				< 0.025	< 0.005
Diabetic STD (4)	576 ± 26	38 ± 9	(8)	2.27 ± 0.17	2.40 ± 0.27
				< 0.001	< 0.001
Diabetic 1% (5)	587 ± 11	285 ± 54	(10)	4.63 ± 0.14	4.08 ± 0.26

Left and right sciatic and tibial nerves were removed for *myo*-inositol determination as described in METHODS.

no significant effect on posterior tibial (SA_f) MNCV measured in the identical animals at 2 wk.

Group III-b (Table 4) animals were of similar age and weight, and were treated identically to group III-a. Plasma glucose and plasma *myo*-inositol values were similar in the two groups with the exception of a slightly lower range of plasma glucose concentrations in the four group III-b diabetic animals fed the standard diet.

Normal tibial nerve *myo*-inositol content exceeded that of sciatic nerve by 32% ($P < 0.025$). Experimental diabetes of a 2-wk duration decreased tibial and sciatic nerve *myo*-inositol content by 34% and 18%, respectively, and abolished the normal *myo*-inositol concentration gradient between tibial and sciatic nerve. Dietary *myo*-inositol supplementation raised both sciatic and tibial nerve *myo*-inositol content (but did not restore the concentration gradient between tibial and sciatic nerve). Thus, 2 wk of dietary *myo*-inositol supplementation produced similar effects on tibial and sciatic nerve *myo*-inositol content but disparate electrophysiologic effects in two populations of motor fibers traversing these nerves in diabetic rats. However, by 4 wk, similar conduction effects were produced by dietary *myo*-inositol supplementation in both groups of fibers.

DISCUSSION

In this study, time-dependent effects of experimental diabetes and dietary *myo*-inositol supplementation on MNCV were assessed in two motor nerve fiber populations: that which innervates the calf muscles (triceps surae) and that which innervates the intrinsic foot muscle. These two populations of large myelinated motor nerve fibers were found to be differentially affected by growth, experimental diabetes, and *myo*-inositol administration. Thus, SK_t MNCV in fibers to the triceps surae was unchanged with growth but was consistently and substantially reduced by acute experimental diabetes; dietary *myo*-inositol supplementation consistently prevented this conduction impairment in the diabetic. In contrast, SA_f MNCV in the fibers to the foot muscles increased with age in both the normal and diabetic (though at a slower rate in the latter), and *myo*-inositol administration reversed rather than prevented this conduction impairment in the diabetic. Since nerve fibers to the calf and foot mus-

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cles occupy the same fascicle in the sciatic nerve during a major portion of their length, such differences are less likely to reflect local environmental factors than inherent differences in these fiber populations.

The widespread use of the highly age-dependent MNCV measurement to the foot muscles in recent studies of experimental diabetes has generated enormous controversy and confusion in the literature. Thomas and co-workers,[6] discussing this prevalent age-related MNCV increase in both the normal and diabetic, concluded that "previous studies on rats (which) have mostly compared diabetic animals with age-matched controls and (which) have used immature animals . . . strongly suggest that the 'reduction' in conduction velocity that has been found is mainly a difference related to retarded maturation in diabetic animals." This objection does not apply to studies that measure conduction velocity to the calf muscles. First, sciatic MNCV recorded in the triceps surae of the rat does not change with age[9] and the reduction in conduction velocity with diabetes represents an absolute rather than relative decrease in MNCV.[2] Second, insulin treatment that reduces but does not normalize plasma glucose fluctuations, but which does promote normal growth, does not improve MNCV to the triceps (see group II insulin-Rx diabetics[2]). Third, dietary *myo*-inositol supplementation prevents or reverses impaired diabetic SK_t MNCV without affecting body weight.[2] Thus, the absolute reduction in SK_t MNCV in the acute SZ-diabetic rat is a direct consequence of the insulin-deficient state mediated in part by secondary alterations in peripheral nerve *myo*-inositol metabolism, and is independent of growth effects.

Despite some differences in the effect of both experimental diabetes and *myo*-inositol supplementation on the SK_t MNCV and SA_f MNCV, there are many similarities. These shared characteristics militate against an exclusively growth-related basis for impaired SA_f MNCV. Thus, impaired SA_f MNCV in rats after 12 wks of untreated SZ diabetes was dramatically improved by 1 wk of rigorous insulin control of hyperglycemia and was normalized by 2 wk[12] a similarly direct relationship between SK_t MNCV and hyperglycemia was previously demonstrated.[2] Furthermore, the great rapidity with which insulin treatment normalized SA_f MNCV after prolonged untreated diabetes further argues against a primary growth effect: other growth parameters such as body mass and organ size would not be corrected so precipitously by insulin treatment.[12] In addition, in the present study, dietary *myo*-inositol ameliorated both impaired SA_f MNCV and SK_t MNCV, although in a delayed fashion in the former, without affecting body weight. These observations suggest a common biochemical component to diabetic conduction impairment in both of these fiber populations that is unrelated to growth.

In two previously published unsuccessful attempts to modify tibial SA_f MNCV in experimentally diabetic rats with dietary *myo*-inositol, older rats were chosen in an attempt to minimize growth-related effects.[5,6] In one study,[5] normal and diabetic plasma glucose concentrations overlapped (estimated ranges from 95% confidence limits were 108–226 and 193–437 mg/dl, respectively). The alterations in sciatic nerve *myo*-inositol content resulting from diabetes or 1% *myo*-inositol diets were insignificant after 4 wk, although they changed in the appropriate direction.[5] MNCV significantly increased by 10% in the normal, decreased 10% in the diabetic, and decreased 8.2% in the *myo*-inositol-supplemented diabetic groups, but the difference between the two diabetic groups was insignificant after 4 wk.[5] However, during the last 2 wk of the study, MNCV increased in 5 of 6 *myo*-inositol-treated diabetics but decreased in 5 of 6 diabetics fed the unsupplemented diets.[5] Although this suggests that more delayed beneficial effects of continuous dietary *myo*-inositol might have occurred, the study was terminated at 4 wk when statistical significance between the diabetic groups was not established.[5] In a second study[6] reported from the same laboratory, tibial MNCV in diabetic rats fed the unsupplemented diet was normal despite the careful exclusion of nonhyperglycemic animals. Thus, the model employed in both studies is not consistently sensitive enough to study subtle metabolically mediated changes in nerve function.[5,6] Whether this deficiency resides primarily in the age of the animals employed or in other experimental conditions is unclear, but it cannot be attributed entirely to the selection of the sciatic-posterior tibial conduction system since this is consistently affected by both experimental diabetes and dietary *myo*-inositol supplementation in younger animals. However, the distal regions of the rat hind-limb peripheral nervous system are particularly prone to age-related degenerative changes.[13] Grover-Johnson and Spencer comment that age-related "axonal abnormalities in rats are not restricted to the plantar nerves, but spread to affect more proximal regions of the affected nerve fibers. That the more proximal axonal changes are associated with the plantar nerve lesion is evident from the absence of these changes in tibial nerve fibers supplying the calf musculature. These nerve fibers, therefore, provide the only region of the tibial/plantar nerve complex where the effects on distal peripheral nerves of chronic toxic/metabolic disease, or of biologic aging, can be seen unimpeded by the effects of the focal plantar nerve lesion."[13] Thus, prominent age-related degenerative processes may limit the sensitivity and/or reproducibility of electrophysiologic studies confined to motor fibers innervating the foot muscles in older rats, and may have obscured the effects of experimental diabetes and dietary *myo*-inositol supplementation.[5,6]

The present study thus demonstrates that a common alteration in *myo*-inositol metabolism may, in part, mediate both tibial and sciatic MNCV impairment in the SZ-diabetic rat. Recently, energy- and sodium-dependent carrier-mediated uptake of *myo*-inositol has been demonstrated in peripheral nerve tissue, which is competitively inhibited by hyperglycemic concentrations of glucose in vitro.[14] It is tempting to speculate that such inhibition may contribute to the effects of experimental diabetes on peripheral nerve *myo*-inositol content and metabolism. However, the delayed improvement in SA_f MNCV in the *myo*-inositol-supplemented diabetic rat is somewhat difficult to reconcile with this view. *Myo*-inositol supplementation commenced with the establishment of diabetes (48 h after streptozocin administration, when hyperglycemia had stabilized). In vitro kinetic studies of *myo*-inositol uptake by peripheral nerve tissue suggest that the plasma *myo*-inositol concentration attained after 2 wk of 1% feeding should saturate the transport system, thereby overcoming the competitive inhibition resulting from hyperglycemia.[14] One might therefore theorize that nerve *myo*-inositol content should have been maintained throughout the experiment. However, the time re-

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quired to establish therapeutic plasma *myo*-inositol levels on the 1% diet is unknown, and transient depletion of nerve *myo*-inositol may occur early in the 2-wk experiment. Furthermore, persistence of *myo*-inositol depletion in some tissue elements is not excluded by the raised sciatic and tibial whole-nerve *myo*-inositol content at 2 wk. Hence, delayed improvement in SA_f MNCV may reflect uncorrected *myo*-inositol depletion in the responsible population of nerve fibers at 2 wk. Alternatively, simple correction of *myo*-inositol depletion may not reverse the resulting conduction defect with equal rapidity in different populations of nerve fibers. The relationship between *myo*-inositol content and fiber conduction may be quite convoluted and complex, involving multiple independent metabolic and physiologic variables such as phosphoinositide metabolism and membrane turnover. These parameters may vary among populations of nerve fibers, thereby determining different rates of functional recovery once *myo*-inositol content is replenished. The nerve fibers to the foot muscles, which mediate SA_f MNCV, are longer, slower conducting, smaller in diameter, and presumably less mature than the fibers to the triceps. Whether any of these characteristics are related to the apparent differences in *myo*-inositol metabolism among various nerve fiber populations is unknown.

An important role for alterations in *myo*-inositol metabolism in the pathogenesis of human diabetic neuropathy has been suggested but never conclusively established.[17,18,26] However, microheterogeneous metabolism of *myo*-inositol or other similar compounds among otherwise closely related populations of nerve fibers might have important relevance to human peripheral nerve disease. Similar metabolic heterogeneity might serve to magnify or reduce the effects of diabetes within specific regions of the human PNS. Such metabolic variability might explain the strikingly early and selective motor involvement of the intrinsic foot muscles in otherwise primarily sensory distal symmetrical diabetic polyneuropathy.

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