Reduced Na^+/K^+ Adenosine Triphosphatase Activity and Motor Nerve Conduction Velocity in L-Fucose–Fed Rats Is Reversible After Dietary Normalization

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Development of early defects in diabetic neuropathy has been linked to metabolic abnormalities and is considered reversible. To further address some of the questions concerning the contribution by metabolic derangements to the development of neural defects and reversibility, we have developed an animal model, by feeding rats a diet containing 20% L-fucose, that develops neural defects similar to those that occur in streptozotocin-induced diabetic rats. After 6 weeks on a 20% L-fucose diet, *myo*-inositol content and Na^+/K^+ adenosine triphosphatase (ATPase) activity of the sciatic nerve were significantly reduced, as was the motor nerve conduction velocity (MNCV). L-Fucose is a monosaccharide that occurs in low concentrations in normal serum but is increased in diabetic patients. In cultured cells, L-fucose, at concentrations that occur in diabetic circulation, is a competitive inhibitor of *myo*-inositol uptake. The purpose of the present study was to compare the sequential pattern of the reversibility of the slowing of MNCV with ouabain-inhibited sciatic nerve Na^+/K^+ ATPase activity and *myo*-inositol content in rats fed a diet containing 20% L-fucose for a period of 6 weeks followed by a normal diet lasting up to 2 weeks. Unbound L-fucose levels in the serum returned to normal in less than 24 hours of the rats being placed on the normal diet. Normalization of slowed MNCV after removing L-fucose–fed rats from the L-fucose diet followed a pattern of recovery similar to the recovery of sciatic nerve ouabain-inhibited Na^+/K^+ ATPase activity, with complete recovery occurring within 7 days of the rats being placed on the normal diet. In contrast, *myo*-inositol content of the sciatic nerve remained decreased following 3 days on the normal diet, and required 14 days for complete normalization. Results from these studies suggest that a causal relationship may exist for reduced Na^+/K^+ ATPase activity and MNCV in L-fucose–fed rats, and that a measurable decrease in *myo*-inositol content may not be necessary for the development of these defects in the sciatic nerve.

REDUCTION in motor nerve conduction velocity (MNCV) is an early defect in diabetic neuropathy.[1-3] Recent studies with diabetic animal models have suggested that both metabolic and vascular defects may contribute to slowing of MNCV.[1-5] Generally, it is thought that hyperglycemia-induced metabolic defects are responsible for the acute and reversible defects in diabetic neuropathy, whereas vascular defects are thought to contribute to long-term, irreversible changes in nerve function and structure. In the sciatic nerve of the streptozotocin-induced diabetic rat, excess glucose is metabolized by the enzyme, aldose reductase, leading to the accumulation of sorbitol and fructose with a reciprocal decrease in *myo*-inositol.[1,6-8] These metabolic changes are accompanied by altered phosphoinositide metabolism, decreased Na^+/K^+ adenosine triphosphatase (ATPase) activity, and slowing of MNCV.[1] In the streptozotocin-induced diabetic rat, these abnormalities are prevented by an aldose reductase inhibitor or by restoring nerve *myo*-inositol levels.[9-17] Additional evidence for a role of *myo*-inositol deficiency in the pathology of diabetic neuropathy arises from our studies of rats fed a diet containing 20% L-fucose.[18] L-Fucose is a levorotatory monosaccharide used by mammalian tissues, and its level and metabolism are altered in diabetes.[19,20] Recent studies from our laboratory using cultured neural cells have shown that L-fucose, at concentrations that occur in diabetic circulation, is a competitive inhibitor of *myo*-inositol transport.[21-23] Feeding rats a diet containing 20% L-fucose caused a decrease in *myo*-inositol content and Na^+/K^+ ATPase activity in the sciatic nerve and a slowing in MNCV.[18] These defects were prevented by supplementing the L-fucose diet with 1% *myo*-inositol.[18] Because L-fucose is not a substrate for aldose reductase, feeding rats a diet containing 20% L-fucose does not lead to accumulation of polyols within the sciatic nerve.[18] Therefore, the L-fucose–fed rat may be a good model to ascertain the contribution of *myo*-inositol deficiency, independent of polyol accumulation, to the development of neural defects associated with diabetic neuropathy.

The purpose of the present study was to analyze the reversibility of neural defects that occur in rats fed a 20% L-fucose diet. The decrease in Na^+/K^+ ATPase activity and MNCV in rats fed a diet containing 20% L-fucose is similar to the decrease observed in diabetic rat models; however, it is unknown if the etiology is the same.[18] These defects, which can develop in rats 3 to 6 weeks after the onset of diabetes, are considered reversible and due to metabolic dysfunctions related to hyperglycemia.[1-3] However, investigation into the reversibility of these defects has been limited because of the lack of a suitable model. The difficulty in normalizing blood glucose in the streptozotocin-induced diabetic rat makes it an impractical model in which to conduct these studies. However, the L-fucose–fed rat model needs only to be placed on a normal diet. Results from studies with rats fed a diet containing 20% L-fucose for 6 weeks followed by a normal diet lasting for up to 2 weeks show that the defects in sciatic nerve Na^+/K^+ ATPase activity and MNCV are significantly improved after

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7 days on the normal diet, and that the patterns of recovery for both properties are similar. Analysis of *myo*-inositol content of the sciatic nerve in these studies shows that *myo*-inositol levels are not totally restored in this period, suggesting that reduced *myo*-inositol content in the sciatic nerve may not be the determining factor for the peripheral nerve defects in L-fucose–fed rats. The effect of hyperglycemia and L-fucose levels on *myo*-inositol transport and phosphoinositide synthesis is discussed.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats aged 7 to 8 weeks and weighing 200 to 225 g were used. Rats were divided into three experimental groups. One group was fed a normal diet (control) repelleted from ground rat chow containing 1% gum xanthan as a binding agent. Two groups were fed a diet containing 20% L-fucose by weight (Pfanstiehl Laboratories, Waukegan, IL). The diets were made by thoroughly blending L-fucose with ground rat chow and 1% gum xanthan. The diets were pelleted and dried in a vacuum oven to a constant weight, and then stored in a cold room (4°C). After 6 weeks, one of the groups receiving the 20% L-fucose diet was placed on the control diet, which was maintained for up to 2 weeks. After the initial 6-week period, some of the rats receiving the normal or L-fucose–containing diet were used to determine MNCV (see below). The rats were then killed, and blood and sciatic nerve samples were collected to determine free and protein-bound serum L-fucose levels and Na^+/K^+ ATPase activity and *myo*-inositol content, respectively. Similar determinations were made after days 1, 3, 7, and 14, with rats reverted to the normal diet after receiving the 20% L-fucose diet for 6 weeks. Analysis of MNCV and sciatic nerve Na^+/K^+ ATPase activity and *myo*-inositol content was also conducted in control and L-fucose–fed rats at these intervals for the purpose of having a positive and negative control for these periods. These latter data were combined with the determinations made after the initial 6-week period. There was no difference in the determinations made for the respective control or L-fucose–fed rats analyzed between 6 and 8 weeks. For all three groups, food and water were provided ad libitum during the entire 8-week experimental period.

Serum Bound and Free L-Fucose Levels

Protein-associated and free L-fucose levels in serum were determined by modifications of the methods described by Djurdjic and Mandic[24] and Cohenford et al,[25] respectively, as adapted by Yorek et al.[18] After determination of MNCV, blood was collected from anesthetized rats by cardiac puncture before killing the animals for tissue collection. The blood was allowed to clot, and serum was obtained following centrifugation. For bound L-fucose determination, 0.2 mL serum was diluted with 1 mL 1-mol/L NaCl, 5 mL ethanol was added, and the samples were vortexed and centrifuged for 5 minutes at 1,000 × *g*. The pellet was resuspended in 1 mL water to which was added 5 mL of a 6:1 mixture of H_2SO_4/H_2O. The samples were then heated in a boiling water bath for 4 minutes, followed by addition of 1 mL CPS reagent (1% L-cysteine-hydrochloride and 0.075% phenol in water). The samples were allowed to cool on ice for 60 minutes, and absorbance was measured at 398 nm and compared with a standard curve prepared similarly using a concentration range of 0 to 600 nmol L-fucose. Unbound L-fucose levels were determined by diluting 0.6 mL serum with 1.5 mL Tris hydrochloride buffer at pH 8.5. The samples were centrifuged in a Centricon 10 Concentrator (Amicon, Beverly, MA), and the filtrate was divided into two 0.6-mL aliquots and lyophilized overnight. One sample was used for a blank and was resuspended in 1 mL Tris buffer and 0.5 mL NAD (10 mmol/L), and the other sample was resuspended in 0.5 mL Tris buffer, 0.5 mL NAD, and 0.5 mL L-fucose dehydrogenase (1 U/5 mL from porcine liver; Sigma, St Louis, MO). Both samples were incubated for 50 minutes at room temperature, and afterward 1.5 mL of a neocuproine-copper reagent (76 mg $CuSO_4$ and 197 mg neocuproine hydrochloride in a 0.2-mol/L sodium acetate buffer, pH 4.7) was added. Absorbance was measured at 455 nm. The concentration of L-fucose was determined by comparison to a standard curve prepared similarly using a concentration of 0 to 400 nmol L-fucose.

MNCV

MNCV was determined as previously described using a noninvasive procedure in the sciatic–posterior tibial conducting system in a temperature-controlled environment.[18] Rats were anesthetized with methoxyflurane. The left sciatic nerve was stimulated first at the sciatic notch and then at the Achilles tendon. Stimulation consisted of single 0.2-millisecond supramaximal (8V) pulses through a bipolar electrode (Grass S44 Stimulator; Grass Medical Instruments, Quincy, MA). The evoked potentials were recorded from the interosseous muscle with a unipolar platinum electrode and displayed on a digital-storage oscilloscope (model 54600A; Hewlett Packard, Rolling Meadows, IL). MNCV was calculated by subtracting the distal from the proximal latency measured in milliseconds from the stimulus artifact of the take off of the evoked potential, and the difference was divided into the distance between the two stimulating electrodes measured in millimeters using a Vernier caliper. MNCV was reported in meters per second.

Sciatic Nerve myo-*Inositol and L-Fucose Content*

The right sciatic nerve was removed, desheathed, and weighed for determination of Na^+/K^+ ATPase activity as described below, and for determination of tissue *myo*-inositol and L-fucose content.[18] For these studies, L-fucose content of the liver and kidney was also determined. Tissue samples were boiled for 10 minutes in water containing α-D-methylmannopyranoside as an internal standard, and were deproteinized with 0.5 mL each of 0.19-mol/L $Ba(OH)_2$ and 0.19-mol/L $ZnSO_4$. Following centrifugation, the supernatant was collected, frozen, and lyophilized. The samples were derivatized and intracellular contents were determined by gas-liquid chromatography as previously described.[18,22]

Na^+/K^+ ATPase Activity

Total and ouabain-inhibited Na^+/K^+ ATPase activities were measured in crude homogenates of sciatic nerve.[12,18] Sciatic nerves were desheathed and homogenized in a polytron, using three 10-second bursts, at 4°C in 1 mL 0.2-mol/L sucrose and 0.02-mol/L Tris hydrochloride buffer, pH 7.5. The samples were then centrifuged at 100 × *g* for 10 minutes at 4°C. An aliquot of the supernatant (50 μL) was added to two cuvettes containing 100 mmol/L NaCl, 10 mmol/L KCl, 2.5 mmol/L $MgCl_2$, 2 mmol/L EGTA, 1 mmol/L Tris-ATP, 1 mmol/L 3-(cyclohexylammonium)phosphoenolpyruvate, 30 mmol/L imidazole hydrochloride buffer (pH 7.3), 0.15 mmol/L NADH, 50 μg lactate dehydrogenase, and 30 μg pyruvate kinase with or without 1 mmol/L ouabain to inhibit the ouabain-sensitive Na^+/K^+ ATPase fraction. After a 20-minute stabilization period, oxidation of NADH was recorded over a 30-minute period. The activity was expressed as micromoles ADP per gram wet weight per hour. Each assay was conducted in triplicate.

Data Analysis

Results are presented as the mean ± SE, and significance of differences was calculated by ANOVA and Student's *t* test.

RESULTS

Effect of L-Fucose Diet on Weight Gain and Serum L-Fucose Levels

Rats were fed a normal diet or a diet containing 20% L-fucose for a period of 6 weeks. Afterward, a set of rats receiving the L-fucose diet were placed on the normal diet for a period of 1, 3, 7, or 14 days (these rats are designated as reversion). The data in Table 1 show that rats receiving a diet containing 20% L-fucose weighed 15% less than control rats after 6 weeks. When the 6-week L-fucose–fed rats were placed on a normal diet they rapidly gained weight, and after 14 days had recovered to the point that their weight was similar to the weight of control rats after the initial 6-week period. The free–L-fucose level in the serum was significantly increased in rats fed a diet containing 20% L-fucose. However, after being placed on a normal diet for only 24 hours, free–L-fucose levels in the serum of rats previously fed 20% L-fucose for 6 weeks were normalized. The reason for the significant decrease in free–L-fucose level in serum of L-fucose–fed rats following 14 days on a normal diet is unknown. However, it could be the result of suppressed synthesis of L-fucose or increased catabolism. As previously reported, protein-bound serum L-fucose levels did not change in 20% L-fucose–fed rats.[18]

Sciatic Nerve Na^+/K^+ ATPase Activity

Feeding rats a diet containing 20% L-fucose for a period of 6 weeks caused a significant decrease in total and ouabain-inhibited Na^+/K^+ ATPase activity (Fig 1). Placing L-fucose–fed rats on a normal diet for 7 days caused a significant improvement in both total and ouabain-inhibited Na^+/K^+ ATPase activity as compared with rats maintained on a diet containing 20% L-fucose. In contrast, the activity of total and ouabain-inhibited Na^+/K^+ ATPase in the sciatic nerve of rats on a control diet for 3 days, after being on a diet containing 20% L-fucose for 6 weeks, remained significantly decreased as compared with control rats.

Table 1. Change in Body Weight and Serum L-Fucose Levels

Animal Group	No. of Rats	Weight (g)*		Serum L-Fucose (mg/dL)	
		Beginning	Final	Free	Bound
Control	24	209 ± 5	381 ± 4	2.13 ± 0.09	37.0 ± 1.8
20% L-fucose	24	212 ± 5	328 ± 8†	3.41 ± 0.20†	36.2 ± 1.6
Reversion					
Day 1	12	212 ± 5	330 ± 6†	2.08 ± 0.15	29.8 ± 1.9
Day 3	12	212 ± 5	335 ± 3†	2.11 ± 0.12	33.7 ± 1.9
Day 7	12	212 ± 5	349 ± 7†	1.88 ± 0.12	35.8 ± 2.5
Day 14	12	212 ± 5	382 ± 7	1.54 ± 0.11†	40.9 ± 2.1

NOTE. Data are the mean ± SE.

*Final weight for control and L-fucose–fed rats was recorded after the initial 6-week period.

†$P < .05$ *v* control.

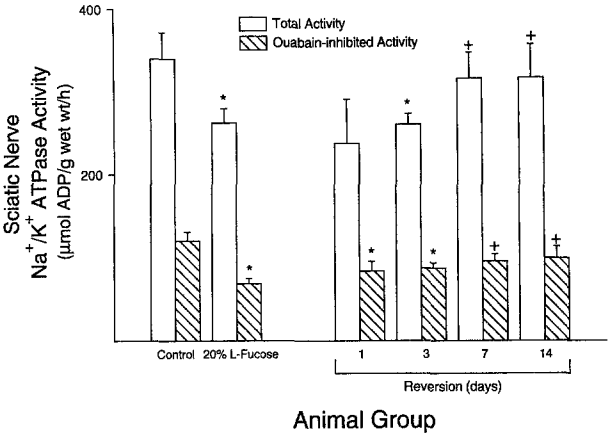

Fig 1. Reversibility of reduced sciatic nerve Na^+/K^+ ATPase activity in rats fed a diet containing 20% L-fucose. Results are the mean ± SE. Data were derived from 24 rats in the control and L-fucose–fed groups and from 12 rats in each of the reversion groups. *$P < .05$ *v* control; †$P < .05$ *v* L-fucose.

MNCV

The data in Fig 2 show that after feeding rats a diet containing 20% L-fucose for a period of 6 weeks, MNCV was significantly slowed. When rats receiving the L-fucose–containing diet for 6 weeks were placed on a normal diet for 7 days, a significant improvement in MNCV was observed, with full restoration occurring in 14 days. An improvement in MNCV was detected after only 3 days on the normal diet, but the change was not significantly different from that in L-fucose–fed rats.

Sciatic Nerve myo-*Inositol Content*

The *myo*-inositol content of the sciatic nerve was significantly decreased in rats fed a diet containing 20% L-fucose for 6 weeks. After 1 and 3 days on the normal diet, *myo*-inositol content of the sciatic nerve remained significantly decreased as compared with control rats. The *myo*-

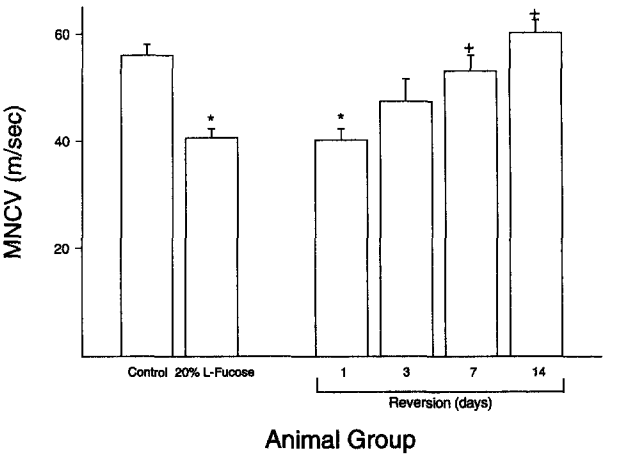

Fig 2. Reversibility of slowed MNCV in rats fed a diet containing 20% L-fucose. MNCV was determined in rats from the same study groups described in Fig 1. *$P < .05$ *v* control; †$P < .05$ *v* L-fucose.

inositol content of the sciatic nerve showed marginal improvement after 7 days on the normal diet, with full restoration occurring after 14 days. Feeding rats a diet containing 20% L-fucose did not cause an increase in the level of L-fucose in the sciatic nerve.[18] However, L-fucose was detected in the kidney and liver. After 6 weeks on the 20% L-fucose diet, the level of L-fucose in the kidney and liver increased from 0.13 ± 0.01 and 0.08 ± 0.01 to 1.14 ± 0.14* and 0.29 ± 0.03* nmol/mg wet weight, respectively (n = 24; *$P < .05$ *v* control). After 1, 3, and 7 days on a normal diet, the level of L-fucose in the kidney of L-fucose–fed rats decreased to 0.26 ± 0.01,* 0.18 ± 0.01,* and 0.12 ± 0.01 nmol/mg wet weight, respectively (n = 12; *$P < .05$ *v* control). In the liver, the level of L-fucose in L-fucose–fed rats after 1 day on a normal diet decreased to near-normal levels, 0.10 ± 0.01 nmol/mg wet weight (n = 12), and remained constant following 3 and 7 days on a normal diet (Fig 3).

DISCUSSION

In a previous study, we had shown that feeding rats a diet containing 10% to 20% L-fucose caused a slowing of MNCV and a decrease in ouabain-inhibited Na^+/K^+ ATPase activity and *myo*-inositol content in the sciatic nerve.[18] Changes that occurred in the neural function of L-fucose–fed rats were similar to the early neural defects that were observed in streptozotocin-induced diabetic rats, and were prevented by supplementing the diet with 1% *myo*-inositol, which replenished nerve *myo*-inositol levels.[6,18,26,27] These studies provided additional evidence that *myo*-inositol deficiency is a contributing factor to the early defects in nerve function associated with diabetic neuropathy. Recent studies suggest that a combination of metabolic abnormalities affecting the nerve and microvascular dysfunction may contribute to the development of diabetic neuropathy.[4-18,28-33] It is believed that the metabolic abnormalities are reversible and may be responsible for the initial defects in nerve function, and may also contribute to the characteristic structural changes that occur in later stages of diabetic neuropathy.[3]

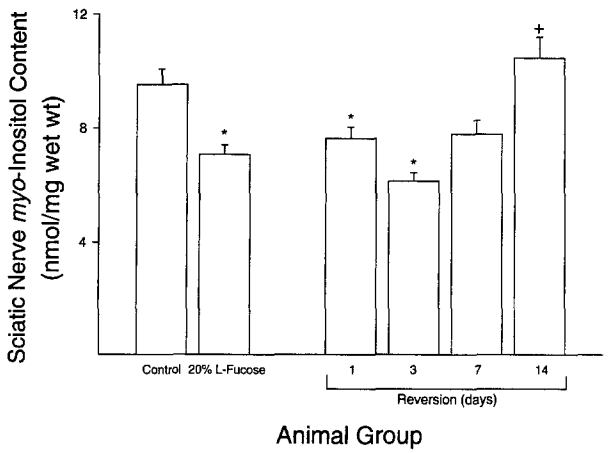

Fig 3. *myo*-Inositol content in sciatic nerve of rats fed a diet containing 20% L-fucose, and reversion after diet normalization. *myo*-Inositol content of sciatic nerve was determined in the same study groups described in Fig 1. *$P < .05$ *v* control; †$P < .05$ *v* L-fucose.

Using streptozotocin-induced diabetic rats, it has been difficult to demonstrate the pathophysiologic sequence and reversibility of metabolic defects associated with the early stages of diabetic neuropathy. In the present study, we have attempted to address this question using rats fed a diet containing 20% L-fucose. The etiology of the neural defects in L-fucose–fed rats is unknown. However, a number of similarities, including deficits in sciatic nerve *myo*-inositol content, reduced Na^+/K^+ ATPase activity, slowing of MNCV, and prevention of these defects by dietary *myo*-inositol, suggest that some factors common to both the streptozotocin-induced diabetic rat and the L-fucose–fed rat may contribute to the neural defects.[1,9,15,18] Therefore, the L-fucose–fed rat may be a useful model to examine questions relating to metabolic derangements associated with diabetic neuropathy. In this study, we have shown that the slowing in MNCV and the decrease in sciatic nerve Na^+/K^+ ATPase activity caused by feeding rats a diet containing 20% L-fucose are reversible by normalizing the dietary conditions. After only 7 days on a control diet, the slowing in MNCV and the decrease in sciatic nerve Na^+/K^+ ATPase activity were significantly improved. Improvement in nerve activity was accompanied by a restoration of sciatic nerve *myo*-inositol levels. However, analysis of the data indicates that the normalization of sciatic nerve *myo*-inositol levels was preceded by the improvement in MNCV and Na^+/K^+ ATPase activity, which occurred almost simultaneously, suggesting that reduced nerve *myo*-inositol content may not be the definitive factor in the development of neural defects seen in L-fucose–fed rats and, by extension, diabetic neuropathy. However, this summation does not exclude *myo*-inositol deficiency from being a contributing factor to the pathological defects associated with diabetic neuropathy. Many studies including our own have clearly shown that *myo*-inositol supplementation of diabetic rats prevents development of many of the neural defects associated with diabetic neuropathy.[18,26,27,34]

The nearly simultaneous recovery in Na^+/K^+ ATPase activity and MNCV suggests that there is a causal relationship between the reduction of Na^+/K^+ ATPase activity and MNCV. This relationship has been supported by some investigators, but is disputed by others.[1,13,18,27,35] Some investigators using assays designed to determine Na^+/K^+-pump activity have concluded that Na^+/K^+ ATPase activity is unchanged in sciatic nerves of diabetic rats.[35] The reason for the discrepancy between these determinations remains to be explained; however, many investigators have determined that Na^+/K^+ ATPase enzyme activity is decreased in sciatic nerves of diabetic rats.[1,2,8,12,13,15,18] Even though the limitations for the measurement of Na^+/K^+ ATPase enzyme activity are well known, the fact that numerous investigators have obtained similar results provides a degree of validity to the results and conclusions.

The second important observation made in these studies is that the recovery of Na^+/K^+ ATPase activity and MNCV in L-fucose rats taken off the diet precedes the normalization of sciatic nerve *myo*-inositol levels. This suggests that a

measurable decrease in *myo*-inositol content of the sciatic nerve may not be necessary to induce a decrease in Na^+/K^+ ATPase activity and/or MNCV. One explanation for these results is that abnormal uptake and metabolism of *myo*-inositol by the sciatic nerve may be a more important factor in neural dysfunction than *myo*-inositol content, which may or may not reflect the current status of tissue *myo*-inositol metabolism. Studies from our laboratory and others have shown that phosphoinositide synthesis is dependent on the uptake of *myo*-inositol.[22,36-38] Phosphoinositides are important elements for regulation of signal transduction pathways, and it has been proposed that abnormal metabolism of phosphoinositides may be a contributing factor to the dysregulation of Na^+/K^+ ATPase activity in the diabetic nerve.[1] Using cultured cells, we have shown that an acute decrease in *myo*-inositol uptake, produced by L-fucose, caused a decrease in Na^+/K^+ ATPase transport activity, which was prevented by maintaining cellular *myo*-inositol uptake by adding a supraphysiological concentration of *myo*-inositol to the medium.[22] In these in vitro studies, the level of *myo*-inositol in cells exposed to L-fucose was unchanged, suggesting that a decrease in *myo*-inositol content was not a factor in the dysregulation of Na^+/K^+ ATPase activity in these neural cells.[22] Rather, the decrease in *myo*-inositol uptake may have altered phosphoinositide metabolism, thereby altering Na^+/K^+ ATPase activity.[22,36,37] Simmons et al[36,37] have proposed that a specific pool of phosphoinositides, dependent on *myo*-inositol uptake, contributes to the regulation of Na^+/K^+ ATPase activity in rabbit aorta. It is possible that a similar mechanism for the regulation of Na^+/K^+ ATPase exists in the sciatic nerve.

Even though the maintenance of sciatic nerve *myo*-inositol content in L-fucose and diabetic rats prevents the development of neural defects in these animal models and supports a role for *myo*-inositol deficiency in the development of diabetic neuropathy, we cannot rule out the possibility that other defects associated with elevated serum L-fucose levels may also contribute to neural dysfunction. One possibility that needs to be addressed is that microvascular dysfunction, which may include abnormal production of nitric oxide, may cause a reduction in blood flow and nerve ischemia.[4,5,28,30,32,33] We do not know if neural microvascular blood flow is decreased in rats fed a diet containing 20% L-fucose; studies are currently in progress to address this question. However, the explanation that a decrease in blood flow is solely responsible for nerve conduction deficits in diabetes does not address the studies that have shown that replenishing *myo*-inositol levels improves nerve function in streptozotocin-induced diabetic rats and corrects some of the paranodal defects in the Bio-breeding rat diabetic model.[18,26,27,34] The most likely outcome from these studies will be that a dual mechanism involving abnormal metabolic pathways and ischemia is responsible for the pathogenesis in diabetic neuropathy.[5]

In summary, L-fucose–fed rats provide another model to study the relationship between metabolic abnormalities and development of neural dysfunctions. In the present studies, we have shown that recovery of sciatic nerve Na^+/K^+ ATPase activity and MNCV precedes normalization of sciatic nerve *myo*-inositol content when rats fed a diet containing 20% L-fucose are placed on a normal diet. At this time, it is not possible to state definitively that these neural dysfunctions are dependent or independent of *myo*-inositol deficiency. Therefore, further study will be necessary to delineate the etiology of neural defects in L-fucose–fed rats and the role of reduced *myo*-inositol metabolism in the development of neural dysfunction.

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