Oral Vanadate Reduces Na^+-Dependent Glucose Transport in Rat Small Intestine

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The effects of oral vanadate supplementation on intestinal morphometry and glucose transport were examined in STZ-induced diabetic and age-matched control male Sprague-Dawley rats. Animals received 0.1 mg/ml vanadium pentoxide in their drinking water over 14 days. Vanadate reduced intestinal glucose maximal transport capacity in both diabetic and control animals. In jejunum tissue, this decrease in glucose absorption was a direct consequence of downregulation of the glucose carrier and was not related to changes in mucosal morphometry. In the ileum tissue of control animals, the vanadate-induced decrease in glucose maximal transport capacity occurred in conjunction with an increase in carrier affinity and mucosal morphometric measurements. In the ileum tissue of diabetic animals, the vanadate-induced decrease in glucose maximal transport capacity occurred with a decrease in mucosal morphometric measurements. Na^+-K^+-adenosine triphosphatase activity was affected by vanadate only in diabetic animals. These results demonstrate that oral vanadate supplementation results in downregulation of the small intestinal sodium-dependent glucose carrier in both diabetic and nondiabetic rats. Furthermore, the vanadate effect may be occurring at the cellular level. *Diabetes* 42:1126–32, 1993

Vanadium is an essential trace element. A vanadium deficiency results in skeletal malformations, increased abortion rates, increased infant mortality rates, delayed body growth, and increased thyroid weight (1). The predominant form of vanadium found in plasma is VO_3-. Transport of vanadate into cells occurs via an anion carrier. Inside the cell, vanadate undergoes a nonenzymatic reduction by glutathione to VO^{2+}.

In skeletal muscle (2) and adipocytes, vanadate mimics the action of insulin by stimulating hexose uptake (3), glucose oxidation (4), glycogen synthase activity (5), lipogenesis (6), and by inhibiting lipolysis (7). Oral vanadate reverses hyperglycemia in both insulin-deficient STZ-treated diabetic rat models (2,8) and hyperinsulinemic rodent models of NIDDM (9). Oral vanadate therapy, with its insulin-mimetic effects, might thus be of adjunctive clinical use not only in maintaining euglycemia but in reducing insulin requirements. The mechanism responsible for the insulin-mimetic effect of vanadate remains to be determined. Vanadate is a structural analogue of phosphate, and the metabolic effects of vanadate are thought to be mediated via alterations in enzyme phosphorylation (10). It has been speculated that vanadate may function as a physiological regulator of Na^+-K^+-ATPase activity through an intracellular redox mechanism (11).

Oral vanadate treatment has been shown to both increase and decrease glucose uptake in rat jejunum (12). Extensive studies have demonstrated that an upregulation of intestinal nutrient and non-nutrient transport occurs during diabetes mellitus (13–15). The consequent increase in intestinal glucose absorption could serve to aggravate diabetes because the enhanced rate of glucose uptake after a meal causes wide fluctuations in serum glucose levels. An agent capable of downregulating glucose transport might even out the postprandial

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STZ, streptozocin; NIDDM, non-insulin-dependent diabetes mellitus; J_{max}, maximal transport capacity; VO_3-, vanadate; VO^{2+}, vanadyl; V_2O_5, vanadium pentoxide; I_{sc}, short-circuit current; 3-*O*-MG, 3-*O*-methyl-D-glucopyranoside; ANOVA, analysis of variance.

glucose response and thereby improve diabetic control. However, if vanadate is to prove useful as oral adjunctive diabetic therapy, characterization of its effects on intestinal Na^+-dependent glucose transport and clarification of its mechanism of action are necessary. We, therefore, examined the effects of vanadate on Na^+-dependent glucose transport in the intestine of diabetic and nondiabetic rats. This allowed the primary effects of vanadate on Na^+-dependent glucose transport in the intestine to be examined in isolation from and compared with secondary intestinal effects manifested in the diabetic intestine.

RESEARCH DESIGN AND METHODS

V_2O_5 was purchased from Fisher Scientific (Edmonton, Alberta, Canada). D-[1-^{3}H(N)]-Glucose (15.5 Ci/mmol) was obtained from DuPont-NEN (Boston, MA). All other chemicals were reagent grade and were obtained from Sigma (St. Louis, MO).

Diabetes was induced in male Sprague-Dawley rats (250–300 g) with a single intraperitoneal dose of STZ (65 mg/kg). Four groups of male Sprague-Dawley rats (250–300 g) were studied: *1*) nondiabetic nonvanadate-supplemented control rats; *2*) nondiabetic vanadate-supplemented control rats; *3*) diabetic nonvanadate-supplemented rats; and *4*) diabetic vanadate supplemented rats. Blood glucose was measured 48 h after injection of STZ and at the time of study using an Ames reflectance photometer and glucose reagent strips (Ames, Miles, Elkhart, IN). Only diabetic rats with hyperglycemia >18.0 mM were entered into the study. Vanadate-supplemented rats received 0.1 mg/ml V_2O_5 dissolved in their drinking water for 14 days. All animals were allowed access to the standard rat diet ad libitum, and housed in an animal care facility with a controlled 12 h light-dark cycle. Studies were conducted on day 15.

Mucosal morphometric assessment. At the time of death, tissue samples were obtained from jejunum and ileum, fixed in 4% paraformaldehyde, embedded in paraffin, and stained with hematoxylin and eosin. Villus and crypt height and width in micromoles per liter were quantitated using a computerized videoplan (Videoplan, Carl Zeiss, Toronto, Ontario, Canada). Protein and DNA content of the mucosa samples were quantitated using the Bradford (16) and Hindgardner (17) methods, respectfully.

Mucosal enzyme analysis. Rats were killed with a sodium pentobarbital overdose (240 μg/kg), the jejunum and ileum were removed, and the luminal contents flushed with ice cold 0.9% NaCl. Mucosa was separated from the underlying muscle by scraping with a glass slide, weighed, and homogenized in 1:10 volume of extraction buffer (50 mM Tris-HCl; 1 mM EDTA; 1 mM phenylmethanesulphonyl fluoride; pH 8.0) using a Polytron homogenizer.

All enzyme assays were based on the protein content of samples as measured by the Bradford technique (16). Sucrase activity was assayed in both homogenate and enriched brush border membrane vesicles using a coupled glucose-6-phosphate dehydrogenase reaction (Boehringer Mannheim, Dorval, Quebec, Canada).

To measure Na^+-K^+-ATPase activity, samples (50 μg protein/ml) were incubated in 25 mM imidazole, 1 mM EGTA, and 0.6 mg deoxycholate/mg protein for 15 min at 37°C to ensure disruption of membranes and access of ligands to all ouabain-binding sites. To start the reaction, aliquots of the homogenate were added to buffer containing 50 mM histidine, 130 mM NaCl, 20 mM KCl, 4 mM MgCl, and 3 mM ATP (pH 7.4). The reaction was allowed to proceed for 15 min at 37°C and then quenched by the addition of ice-cold 8% perchloric acid. Samples were centrifuged, and the inorganic phosphate levels were measured using the method of Radominski-Pyret et al. (18). Samples to which protein was added after the reaction was terminated were used as blanks. Na^+-K^+-ATPase activity was calculated as the difference between inorganic phosphate released in the presence and absence of ouabain. Ouabain-sensitive ATP hydrolysis was in the range of 7–22% of total ATP hydrolysis and did not differ between the four groups.

Intact tissue transport experiments. Segments of jejunum and ileum from which the outer muscle layer had been removed were mounted in Ussing chambers and bathed on both sides with a bicarbonate-Ringer's solution containing 20 mM fructose circulated with 5% CO_2-95% O_2 (pH 7.4) at 37°C. Trans-epithelial potential difference, resistance, and I_{sc} were measured as described previously (19). Changes in J_{max} and carrier affinity (K_m) were determined for 3-*O*-MG (concentration range 0.5–60 mM) by measurement of concentration-dependent I_{sc}.

Brush border membrane transport experiments. Brush border membrane vesicles were prepared from the proximal (jejunal) and distal (ileal) half of the small intestine of both control and nondiabetic vanadate-supplemented rats using the calcium chloride precipitation method described by Kessler et al. (20). Purification was assessed by measuring sucrase-specific activity in the original homogenate and in the final preparation. Similarly, basolateral membrane contamination was monitored by assaying Na^+-K^+-ATPase activity.

Glucose uptake measurements. D-Glucose uptake studies were conducted using a modification of the rapid filtration technique of Hopfer et al. (21). Under the conditions used in these experiments, preliminary studies demonstrated that rates of glucose uptake were linear up to 10 s, that the overshoot peaked at 25 s, and that uptake reached equilibrium at 2 min. Therefore, an incubation time of 5 s was used to estimate initial glucose uptake rates for concentrations of glucose ranging from 10 μM to 4 mM. To start the reaction, 10 μl of freshly prepared vesicles in a buffer containing 250 mM mannitol, 10 mM HEPES, and 10 mM Tris (pH 7.5) were added to 50 μl of incubation buffer, which contained 100 mM NaSCN, 50 mM mannitol, 20 mM HEPES, and varying concentrations of D-[^{3}H]glucose (pH 7.5). The diffusional component of uptake was measured by replacing 100 mM *cis*-NaSCN with an equivalent concentration of potassium thiocyanate. This component was subtracted from total uptake to give the Na^+-dependent D-glucose uptake rate. The reaction was stopped by the addition of 2 ml of ice-cold stop solution (20 mM HEPES, 100 mM

TABLE 1
Animal profile

	Control group	Control vanadate group	Diabetic group	Diabetic vanadate group
Food intake (g/day)	31.4 ± 2.0	33.2 ± 2.0	41.5 ± 2.1*	27.7 ± 1.8
Water intake (ml/day)	46.1 ± 0.5	45.5 ± 2.0	134.7 ± 39.6*	46.4 ± 1.3
Weight gain (g/day)	6.7 ± 1.0	6.2 ± 1.0	2.2 ± 1.5*	2.9 ± 1.4*
Serum insulin (μU/ml)	91.4 ± 13.8	83.2 ± 22.4	21.3 ± 3.0*	18.1 ± 4.0*
Serum glucose (mM/L)	4.8 ± 0.2	5.1 ± 0.3	>18*	12.9 ± 0.6*

Data are means ± SE of 8 animals in each group.
*P < 0.02 vs. control animals.

NaCl, and 150 mM mannitol). The resultant mixture was filtered through a prewetted and chilled 0.45 μm nitrocellulose filter (Millipore, Mississauga, Ontario, Canada) and washed with 8 ml of ice-cold stop solution. Filters were then dissolved in vials containing 5 ml of scintillation fluid. Nonspecific binding of [^{3}H]glucose to filters was measured by filtration of the incubation medium, stop solution, and vesicles (without allowing mixing of medium and vesicles). All results were subsequently corrected for nonspecific binding. The volume of vesicles was routinely measured during each transport study by incubating vesicles with medium for 2 h. The final volume of vesicles ranged from 0.2 to 1 μl/mg protein and did not differ between groups. Experiments were performed on at least four different freshly prepared vesicle preparations on different days. Uptake data are reported as nanomoles of glucose per minute per milligram of vesicle protein.

Statistical and kinetic analysis. Statistical analysis was performed using the SYSTAT statistical software package (Evanston, IL). Differences between means were evaluated using ANOVA and the Student's t test where appropriate. Curve fitting and parameter estimation for nonlinear relationships were performed with data points weighted inversely to within sample variances at each concentration (22).

RESULTS

Animal profile. The vanadate-supplemented control group did not demonstrate altered food or water intake, weight gain, or serum insulin or glucose levels relative to control animals (Table 1). Diabetic animals showed increased food and water intake and serum glucose levels and decreased weight gain and serum insulin levels relative to controls (Table 1). Vanadate supplementation of diabetic animals lowered blood glucose and normalized food and water intake, whereas serum insulin levels and weight gain remained unaltered.

Mucosal morphometric assessment. Jejunal mucosal wet weight, DNA, protein, protein-to-DNA ratio (Table 2), villus height, and crypt depth (Fig. 1) were not affected by either diabetes or vanadate supplementation. In the ileum, vanadate supplementation in control animals significantly increased mucosal wet weight, DNA, protein (Table 2), villus height, and crypt depth (Fig. 1) relative to control animals, whereas the protein-to-DNA ratio was unchanged (Table 2). In contrast, vanadate supplementation in diabetic animals decreased the diabetic-induced elevation of mucosal wet weight, DNA, protein (Table 2), and villus height (Fig. 1) without changing the protein-to-DNA ratio.

Intact tissue transport studies. Jejunal and ileal transport of 3-*O*-MG were measured by adding increasing amounts of solute to the mucosal side of the samples mounted in Ussing chambers. The resultant increase in I_{sc} reflects an increase in 3-*O*-MG–stimulated sodium-dependent cotransport (16).

***3-O*-MG transport.** In jejunum tissue, 3-*O*-MG transport was similar in control and diabetic animals (Table 3).

TABLE 2
Mucosal weight and composition

	Control group	Control vanadate group	Diabetic group	Diabetic vanadate group
Jejunal mucosa				
Wet weight (mg/cm)	67.2 ± 5.8	62.8 ± 4.5	78.6 ± 5.3	74.3 ± 5.6
DNA (mg/cm)	2.3 ± 0.2	2.5 ± 0.4	2.7 ± 0.3	2.7 ± 0.4
Protein (mg/cm)	4.6 ± 0.5	5.6 ± 0.5	6.9 ± 0.5	5.9 ± 0.4
Protein-to-DNA ratio (mg/mg)	2.0 ± 0.2	2.2 ± 0.2	2.5 ± 0.3	2.2 ± 0.4
Ileal mucosa				
Wet weight (mg/cm)	70.0 ± 5.4	81.5 ± 6.3*	85.2 ± 5.8*	73.9 ± 4.1†
DNA (mg/cm)	1.1 ± 0.2	1.7 ± 0.5*	1.9 ± 0.3*	1.4 ± 0.4†
Protein (mg/cm)	4.5 ± 0.1	5.6 ± 0.3*	7.3 ± 0.8*	5.7 ± 0.6†
Protein-to-DNA ratio (mg/mg)	4.1 ± 0.1	3.6 ± 0.5	3.8 ± 0.4	4.1 ± 0.3

Data are means ± SE of 8 animals in each group.
*P < 0.05 compared with control animals.
†P < 0.05 compared with diabetic animals.

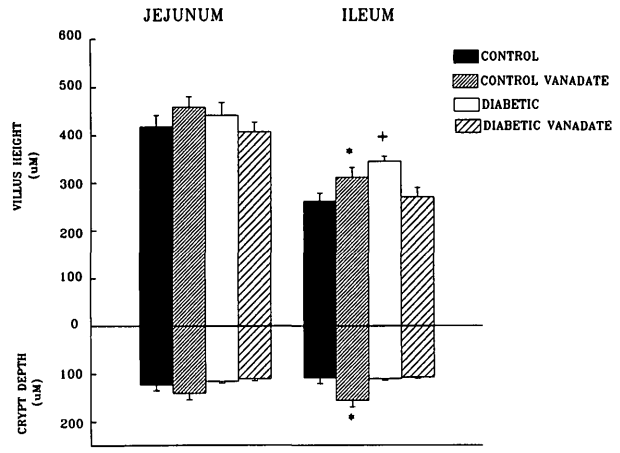

FIG. 1. Villus height and crypt depth in jejunum and ileum tissue of control, vanadate-supplemented control, diabetic, and vanadate-supplemented diabetic animals. Data are means ± SE. *$P < 0.05$ compared with control and vanadate-supplemented diabetic animals. +$P < 0.02$ compared with control and vanadate-supplemented diabetic animals.

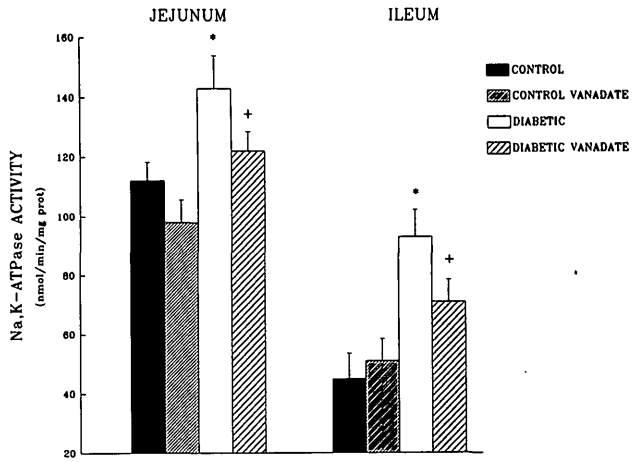

FIG. 2. Na^+-K^+-ATPase activity in jejunum and ileum tissue of control, vanadate-supplemented control, diabetic, and vanadate-supplemented diabetic animals. Data are means ± SE. *$P < 0.02$ compared with control, vanadate-supplemented control, and vanadate-supplemented diabetic animals. +$P < 0.05$ compared with control and vanadate-supplemented control animals.

Vanadate supplementation in both control and diabetic animals reduced jejunal 3-*O*-MG J_{max} with no change in K_m. This change in jejunal 3-*O*-MG transport occurred without changes in jejunal mucosal morphometry. In the ileum, diabetes increased 3-*O*-MG transport twofold. Vanadate supplementation in diabetic and control animals significantly reduced ileal 3-*O*-MG J_{max}. The vanadate-induced change in ileal transport occurred in conjunction with a fall in 3-*O*-MG K_m (increased carrier affinity) and paralleled morphometric changes in the vanadate-supplemented diabetic but not vanadate-supplemented control groups.

Na^+-K^+-ATPase activity. In the small intestine, the transepithelial sodium electrochemical gradient is maintained by Na^+-K^+-ATPase activity on the basolateral surface. Measurement of Na^+-K^+-ATPase total activity in tissue homogenate provides an indication of an altered in vivo sodium electrochemical gradient. In general, ileum tissue had a lower Na^+-K^+-ATPase activity compared with jejunum tissue in all groups (Fig. 2). Vanadate supplementation in control animals did not affect Na^+-K^+-ATPase total activity in either the jejunum or the ileum tissues. Diabetes raised jejunal and ileal Na^+-K^+-ATPase activity. Vanadate supplementation in diabetic animals significantly lowered both jejunal and ileal Na^+-K^+-ATPase levels to near control levels. Thus, a vanadate-induced inhibition of Na^+-K^+-ATPase activity is unlikely to be responsible for the decreased 3-*O*-MG transport in control animals; however, it may have contributed to the decreased 3-*O*-MG transport in the diabetic animals.

Brush border membrane experiments.

Purification and validation. To confirm that the reduction in 3-*O*-MG transport occurred at the level of the Na^+-dependent glucose carrier, brush border membrane glucose transport was assessed in control animals. Brush border membrane purification, on the basis of enrichment of sucrase activity and contamination by basolateral membranes as measured by Na^+-K^+-ATPase activity, was similar in each group (Table 4).

Brush border membrane glucose uptake. Figure 3 illustrates Na^+-dependent rates of D-glucose uptake into brush border membrane vesicles from proximal (jejunal; Fig. 3*A*) and distal (ileal; Fig. 3*B*) intestine. These data have been corrected for rates of transport observed in the absence of a sodium gradient. Similar to results in intact tissue, vanadate supplementation decreased glucose uptake in both jejunal and ileal brush border mem-

TABLE 3
Kinetic constants for 3-*O*-MG transport in intact tissue

	Control group	Control vanadate group	Diabetic group	Diabetic vanadate group
Jejunum				
J_{max} (μA/cm²)	48.3 (40,56)	40.4 (35,46)*	49.5 (42,56)	40.7 (36,44)†
K_m (mM)	31.5 (20,43)	31.0 (21,42)	37.9 (25,50)	23.9 (19,28)
Ileum				
J_{max} (μA/cm²)	26.4 (24,29)	18.2 (17,19)*†	42.1 (34,46)*	33.1 (31,36)†
K_m (mM)	20.3 (16,25)	12.3 (9,15)*†	35 (23,48)	14.9 (9,20)†

Data are means of 8 animals in each group. (95% confidence limits), calculated by nonlinear regression analysis.
*$P < 0.05$ compared with control animals.
†$P < 0.05$ compared with untreated diabetic animals.

TABLE 4
Enzymatic characteristics of brush border membrane preparations

	Sucrase (U/mg protein)			Na^+-K^+ ±ATPase (nm · min^{-1} · mg $protein^{-1}$)		
	Homogenate	Brush border membrane vesicles	Fold*	Homogenate	Brush border membrane vesicles	Fold*
Jejunum						
Control group	0.19 ± 0.03	2.87 ± 0.82	15.1	123 ± 11	103 ± 12	0.84
Control group	0.21 ± 0.04	3.07 ± 0.74	14.6	98 ± 13	71 ± 12	0.73
Ileum						
Control group	0.11 ± 0.02	1.47 ± 0.31	13.4	41 ± 8	26 ± 6	0.65
Vanadate group	0.13 ± 0.03	1.64 ± 0.42	12.6	51 ± 9	36 ± 8	0.70

Data are means ± SE of 8 animals.
*Purification values represent brush border membrane specific activity/homogenate specific activity.

brane vesicles. Kinetic parameters as determined by nonlinear regression analysis are given in Table 5. Vanadate supplementation reduced jejunal J_{max} and K_m 2.4- and 1.7-fold and ileal J_{max} and K_m 4.6- and 13.1-fold, respectively.

DISCUSSION

In diabetic rats, intestinal absorption of glucose increases as a result of an elevation in the number of glucose transporters (23) and a decrease in the rate of enterocyte glucose utilization (24). The signal responsible for this increase is unknown, although both serum insulin and glucose levels have been implicated (25). In agreement with previous studies (26), we found that oral vanadate supplementation prevented the occurrence of intestinal transport changes normally seen in STZ-induced diabetic rats. However, in a diabetic model, it is difficult to determine whether the decreased glucose absorption occurs as a direct result of the effects of vanadate on the intestinal enterocyte or as a secondary response caused by the lowering of blood glucose levels. Data obtained from this study suggest that vanadate directly affects both the jejunum and the ileum at the cellular level reducing Na^+-dependent glucose uptake in the absence of any change in food intake or serum glucose and insulin levels.

In the small intestine, Na^+-dependent glucose uptake is dependent on the presence of a sodium electrochemical gradient that is maintained by Na^+-K^+ATPase activity on the basolateral membrane. Vanadate is a potent inhibitor of purified Na^+-K^+-ATPase, producing 50% inhibition at concentrations of 10^{-7} to 10^{-8} (28). Based on a 40% absorption rate (29), rats in this study absorbed a total of 1.6 mg of vanadate, which would accumulate primarily in the liver and kidney (29). Under physiological conditions, however, internalized VO_3- (a potent Na^+-K^+-ATPase inhibitor) is reduced intracellularly to VO^{2+}, a species that is very ineffective in inhibiting the enzyme (11).

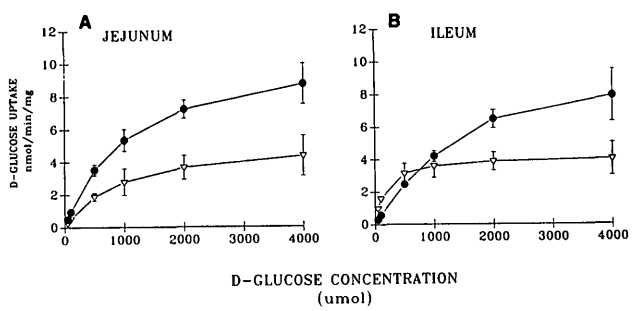

FIG. 3. Initial rates of D-glucose uptake in brush border membrane vesicles as a function of D-glucose concentrations in medium for jejunum (*A*) and ileum (*B*) of control (▽) and vanadate-treated (●) animals. Results represent the difference between rates of D-glucose uptake seen in the presence and absence of sodium. Each data point represents means ± SE of 6 separate membrane preparations from both groups. Lines were drawn using best fit curve analysis.

Conflicting data exist about the effects of oral vanadate on intestinal Na^+-K^+-ATPase activity. We found that the oral dose of vanadate used in this study (0.1 mg/ml) had no effect on intestinal mucosal Na^+-K^+-ATPase activity in the nondiabetic animals. This is in agreement with Higashina et al. (30) but not with Hajar et al. (12), who observed decreased activity of Na^+-K^+-ATPase activity in the intestine. This may be related to two factors. First, Hajar et al. (12) used sodium metavanadate, whereas V_2O_5 was used in this study. These two compounds have different solubilities, toxicity, and speed of elimination (31), which would likely result in different concentrations of intracellular vanadate. Second, the duration of treatment differed from 30 days in the study of Hajar et al. (12) to 14 days in this study. Because ingested vanadate can be retained and accumulated by the small intestine for up to 16 days after a single dose (30), a longer period of treatment would likely result in higher intracellular vanadate concentrations. An accurate measurement of not only the total intracellular vanadate concentration but also its oxidative state would be necessary to determine if orally ingested vanadate is actually inhibiting Na^+-K^+-ATPase. An alternative explanation for any observed changes in Na^+-K^+-ATPase activity is that any decreased activity may actually be a secondary cellular response to a decrease in Na^+-dependent solute absorption across the brush border, rather than the primary cause of the decrease in Na^+-dependent glucose transport.

Vanadate-supplemented animals demonstrated a decrease in K_m, which indicates an increased affinity of the glucose transporter for glucose at the intact tissue level in

TABLE 5
Kinetic constants for D-glucose uptake in brush border membrane vesicles

	Control group		Control vanadate group	
	Jejunum	Ileum	Jejunum	Ileum
J_{max} (mM)	12.3 (−1.3,25.9)	20.8 (−1.4,4.4)	5.2 (2.1,8.4)*	4.5 (3.0,6.1)*
K_m (mM)	1.52 (−1.4,4.4)	3.76 (−3.3,10.8)	0.90 (−0.7,1.9)*	0.29 (0.15,0.43)*

(95% confidence limits), calculated by nonlinear regression analysis.
*$P < 0.05$ relative to control animals.

the ileum and brush border membrane level in both jejunum and ileum of nondiabetic rats. Meddings et al. (32) have shown transporter affinity to be altered by changes in membrane physical composition. Although there has been no full study of vanadate-induced membrane changes, reports exist that vanadate may alter polyunsaturated fatty acid content in membranes, thus having an antioxidant effect (33). The mechanism by which vanadate could induce the alterations of membrane structure may involve changes in cholesterol and lipid biosynthesis and/or metabolism. The altered affinity observed in this study for the Na^+-dependent glucose carrier lends support to the idea that oral vanadate supplementation alter membrane composition. Additional studies will be necessary, however, to clarify these changes.

Although previous studies have implied that vanadate's induction of euglycemia in diabetic animals occurs as a result of enhanced uptake of circulating glucose into adipocytes and skeletal muscle (2–5), this study demonstrates that this enhancement probably represents only a portion of the overall effect of vanadate. The concentration of vanadate we used (0.1 mg/ml) was not sufficient to normalize completely the serum glucose levels but was able to prevent intestinal glucose transport changes from occurring, indicating a possible direct cellular effect in the intestine. In addition, the results obtained from brush border membrane vesicles show that vanadate directly reduces glucose absorption across individual enterocytes, thus causing decreased glucose absorption, particularly in the proximal small intestine. As a result, more luminal glucose would reach the distal small intestine, a site not normally involved in glucose absorption. The altered surface area observed in the distal small intestine of vanadate-supplemented control animals is probably caused by an increased exposure to glucose, as the intestine responds to increased luminal glucose concentrations with an increase in surface area (34). In a similar fashion, the diabetic animals supplemented with vanadate showed a decrease in food intake and a subsequent decrease in surface area. For diabetic animals, the overall result of this process would be better control of diabetes as a result of the delay in intestinal glucose absorption and the blunting of the postprandial glycemic response.

In conclusion, oral vanadate supplementation results in a downregulation of Na^+-dependent glucose transport in both jejunum and ileum tissue, probably through a direct mediation at the cellular level. Adjunctive oral vanadate may thus prove useful in the management and control of diabetes.

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