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Changes in amino acid and glucose transport in brush-border membrane vesicles of hyperglycemic guinea-pig small intestine

Osamu Satoh, Shin-ya Koyama, Kazuo Yamada and Takashi Kawasaki

Department of Biochemistry, Hiroshima University School of Medicine, Kasumi, Minami-ku, Hiroshima (Japan)

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Changes in intestinal transport of L-amino acid and D-glucose in streptozotocin (STZ)-induced hyperglycemic guinea-pig were examined using brush-border membrane vesicles. The vesicles were prepared from guinea-pigs on days 3, 10, and 21 after intravenous injection of STZ (150 mg/kg body weight), and from control animals injected with sodium citrate buffer (pH 4.5) in the same manner. Blood glucose concentration rose to greater than 300 mg/dl in the hyperglycemic guinea-pigs 24 h after STZ injection, and then remained constant. All vesicles obtained under different conditions showed a similar specific activity of alkaline phosphatase, a marker enzyme of the intestinal brush-border membrane, indicating a similar purity of the membrane vesicles. On day 3, Na^+-dependent amino acid transport was found to be approx. 30% higher in the hyperglycemic than in the control group, and Na^+-dependent glucose transport was 35% lower in the hyperglycemic than in the control group. On days 10 and 21, Na^+-dependent amino acid transport had recovered to the control levels, whereas Na^+-dependent glucose transport was twice as high as in the hyperglycemic than in the control group. Na^+-independent amino acid and Na^+-independent glucose transport showed no difference between the hyperglycemic and control groups after STZ injection. The changes in both Na^+-dependent amino acid and glucose transport were attributed to significant changes in the V_{max} values with no change in the apparent K_m values. This study clearly demonstrates that hyperglycemia is associated with reciprocal changes in intestinal transport of amino acid and glucose in its acute phase, suggesting an important pathophysiological regulatory mechanism for absorption of nutrients by control of the numbers of specific carriers.

Introduction

Amino acid and glucose transport across the epithelial cells of the small intestine involve two processes: transport from the gut across the brush-border membrane, and exit into the blood across the basolateral membrane. Intestinal transport systems for amino acids have been described in brush-border membrane vesicles of rabbit, and involve passive diffusion and Na^+-dependent (NBB, IMINO, PHE) and Na^+-independent (y^+, L) systems [1–3]. We have more recently reported that guinea-pig small intestinal brush-border membrane vesicles contain at least three Na^+-dependent (imino, glycine, neutral) and at least three Na^+-independent (neutral, acidic, cationic) carrier systems [4,5].

D-Glucose is actively transported with Na^+ by a specific carrier across the intestinal brush-border membrane [3], and the molecular structure of the glucose carrier has been described [6].

The small intestine is capable of adapting its nutrient transport to numerous physiological, pathophysiological and environmental requirements. Intestinal amino acid and glucose transport is known to be increased in various disease states and physiological conditions [7,8]. In the chronically diabetic rat, specific binding studies have indicated a higher total number of amino acid [9,10] and glucose [8,11–14] carriers in the small intestine compared with controls. However, in genetically diabetic mice, amino acid and glucose transport by isolated small intestinal brush-border membrane vesicles was not altered [15].

It is important to investigate whether the changes in amino acid transport systems characterized in guinea-pig small intestine [5], occur in association with metabolic

Abbreviations: STZ, streptozotocin; Hepes, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; transport systems NBB, IMINO, PHE, y^+ and L, see Ref. 2.

Correspondence: T. Kawasaki, Department of Biochemistry, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan.

disorders. We have therefore investigated the time-dependent changes in amino acid transport as well as glucose transport in small intestinal brush-border membrane vesicles prepared from guinea-pigs made hyperglycemic by streptozotocin (STZ) injection. Reciprocal regulation of amino acid transport and glucose transport occurred for a short period of time after induction of hyperglycemia; the Na^+-dependent amino acid transport then returned to the control level, and the Na^+-dependent glucose transport increased to twice the control level.

Materials and Methods

Preparation of hyperglycemic guinea-pigs. STZ-induced hyperglycemic guinea-pigs were prepared according to the method of Brosky et al. [16]. Male guinea-pigs, weighing 400–600 g, were fasted for 24 h and then injected subcutaneously with 20–25 IU of insulin. When signs of hypoglycemia such as muscle twitching and extreme weakness developed, STZ (150 mg/kg body weight) dissolved in sodium citrate buffer (pH 4.5) was injected through the dorsal vein of the penis. The animals were then force-fed via a stomach tube to prevent hypoglycemic convulsions. Glycosuria and hyperglycemia developed on the second day after the injection of STZ. The control group of animals was starved for 24 h and injected with sodium citrate buffer (pH 4.5) used in solving STZ. Blood glucose concentration was determined using an automatic glucose analyzer, REFLOLUX-S (Boehringer Mannheim Yamanouchi Co., Tokyo).

Isolation of membrane vesicles. Membrane vesicles were prepared from the guinea-pig small intestine by the procedure of Fujita et al. [17] with slight modification as described previously [5], in which 0.25 M sucrose was replaced by 0.32 M sucrose as the sucrose-EDTA buffer. The final pellet was suspended in 2 mM Tris-Hepes buffer (pH 7.5) containing 100 mM D-mannitol and 0.1 mM $MgSO_4$, to give a final protein concentration of approx. 3–4 mg/ml. The membrane vesicle preparation showed an approximately 10–12-fold increase in alkaline phosphatase and sucrase compared to the initial homogenates, while the specific activity of Na^+/K^+-ATPase (ouabain-sensitive) was decreased by one-fifth [5].

Transport method. All assays of transport activity were carried out with 20 μM substrate at 25°C according to the procedure described previously [5]. The membrane vesicles were preincubated in a medium containing 50 mM D-mannitol, 5 mM Tris-Hepes (pH 7.5), and 50 μM $MgSO_4$ at 25°C for 5 min. Transport was initiated by the addition of labeled substrate, and incubation was continued at 25°C for the period described in the text. Other additions are described in the figures. The transport of substrate was terminated by diluting an aliquot of the sample with a 40-fold excess of ice-cold buffer composed of 150 mM NaCl, 50 mM $MgCl_2$, 30 mM D-mannitol, and 10 mM Tris-Hepes buffer (pH 7.5). The diluted sample was immediately filtered through a Millipore cellulose filter (0.45 μm) and washed with 3 ml of the same ice-cold buffer. Radioactivity retained on the filter was counted using liquid scintillation [18].

For all L-amino acid and D-glucose transport tested, the transport for the first 5 s was linear and was used as the initial velocity unless otherwise indicated. These assay conditions for Na^+-dependent, Na^+-independent, and diffusional transport of a given substrate have been described in our previous paper [5]. Briefly, Na^+-dependent transport of a given substrate was expressed by subtracting the transport in the presence of 100 mM KCl from that in the presence of 100 mM NaCl. Na^+-independent and carrier-mediated transport was expressed by subtracting the diffusional component of the transport in the presence of 100 mM KCl. The diffusional component of a substrate was determined by measuring the influx in the presence of 30 mM unlabeled substrate in addition to 100 mM KCl.

Alkaline phosphatase activity. Alkaline phosphatase, one of the brush-border marker enzymes, was assayed using 2 mM *p*-nitrophenyl phosphate as the substrate at pH 10.0 (100 mM glycine-NaOH buffer) and 37°C [17].

Protein estimation. The protein concentration of the vesicle preparation was determined by the method of Lowry et al. [19] using bovine serum albumin as a standard.

Chemicals. All reagents were of the highest purity commercially available. The labeled amino acids and glucose were purchased from New England Nuclear, and streptozotocin from Sigma Chemical Co.

Results

Blood glucose concentration in guinea-pigs given STZ

Table I shows blood glucose concentrations of control and STZ-induced hyperglycemic guinea-pigs. Blood

TABLE I

Blood glucose concentration

Guinea-pigs weighing 400–600 g were injected intravenously with streptozotocin (STZ) dissolved in sodium citrate buffer (pH 4.5) at 150 mg/kg (hyperglycemia). On days 3, 10, and 21 the animals were killed and blood glucose concentrations were determined as described in Materials and Methods. Values are expressed as mean ± S.D. for three experiments.

Days	Blood glucose (mg/dl)	
	control	hyperglycemia
3	98 ± 5	312 ± 14
10	102 ± 4	298 ± 32
21	109 ± 4	355 ± 30

glucose concentrations were significantly elevated to similar levels in all hyperglycemic guinea-pigs days 3, 10, and 21 after STZ injection. Body weight and food intake were not significantly different in the control and hyperglycemic groups (data not shown).

Purity of the intestinal brush-border membrane vesicles

The specific activity of alkaline phosphatase, a marker enzyme of brush-border membrane, was similar in all the vesicles prepared from age-matched STZ-treated and untreated animals (Table II). Both groups showed an approximately 12-fold increase in alkaline phosphatase compared to the initial homogenates, indicating a similar purity of the vesicle preparations.

L-Amino acid and D-glucose transport in small intestine of the control and hyperglycemic groups

Changes in L-amino acid and D-glucose transport day 3 after STZ injection. Seven labeled amino acids were selected as representative substrates for the transport systems classified in the previous paper [5]: L-proline for the imino acid system (Na^+-dependent); glycine for the glycine system (Na^+-dependent); L-alanine, L-phenylalanine, and L-leucine for the neutral amino acid system (Na^+-dependent > Na^+-independent); L-aspartic acid for the acidic amino acid system (Na^+-independent); L-lysine for the cationic amino acid system (Na^+-independent). Table III shows the initial rates of L-amino acid and D-glucose transport measured in control and hyperglycemic guinea-pig intestinal membrane vesicles day 3 after STZ injection. Na^+-dependent L-proline transport was 30% higher in the hyperglycemic animals than in the control animals. This small, but significant increase of Na^+-dependent L-proline transport in the hyperglycemic vesicles was reproducibly detected during an uptake period during which a Na^+ gradient (out > in) was detected (Fig. 1a). Na^+-dependent glycine transport as well as Na^+-dependent L-alanine, L-phenylalanine, and L-leucine transport were also 30% higher in the hyperglycemic group than in the control group. However, the Na^+-independent transport of neutral amino acids, L-aspartic acid, and L-lysine did not differ between control and hyperglycemic vesicles. The increases in Na^+-dependent transport (approx. 30%) were similar in the three systems. It is interesting that Na^+-dependent transport of D-glucose in the hyperglycemic group was 35% lower than that in the control day 3 after STZ injection. However, the Na^+-independent transport rate of D-glucose did not differ between the two groups (Table III).

Changes in L-amino acid and D-glucose transport day 10 after STZ injection. By day 10 after STZ injection, Na^+-dependent amino acid transport enhanced by hyperglycemia had decreased to the control level, and Na^+-independent transport of all amino acids tested was not affected in both groups (Table IV). That is, all amino acids tested showed their individual basal transport, which was not influenced by hyperglycemia day 10 after STZ injection. However, Na^+-dependent transport of D-glucose in the hyperglycemic group was 85% higher than that in the control group, with no difference in the rate of Na^+-independent D-glucose transport between the two groups.

L-Amino acid and D-glucose transport day 21 after STZ injection. Transport activities determined day 21

TABLE II

Alkaline phosphatase activity of brush-border membrane vesicles from control and hyperglycemic guinea-pig small intestine

Alkaline phosphatase, a marker enzyme of the brush-border membrane, was assayed using *p*-nitrophenyl phosphate as a substrate at pH 10.0 and 37 °C [17]. Values are expressed as mean ± S.D. for three experiments.

Days	Alkaline phosphatase (μmol/mg protein per min)	
	control	hyperglycemia
3	2.25 ± 0.14	2.48 ± 0.33
10	2.35 ± 0.45	2.27 ± 0.31
21	2.22 ± 0.36	2.29 ± 0.47

TABLE III

L-Amino acid and D-glucose transport into brush-border membrane vesicles prepared day 3 after STZ injection

The initial transport rates of seven L-amino acids and D-glucose were measured. Membrane vesicles were suspended in a medium containing 100 mM D-mannitol, 0.1 mM $MgSO_4$, and 2 mM Tris-Hepes (pH 7.5). Transport was initiated by adding 50 μl of membrane suspension (3–4 mg protein/ml) to 60 μl of incubation medium, obtained by mixing 10 μl of 220 μM labeled substrate (final concentration: 20 μM) with 50 μl of 110 mM D-mannitol, 110 μM $MgSO_4$, 11 mM Tris-Hepes (pH 7.5), and 220 mM NaCl ($V_{(Na)}$) or 220 mM KCl ($V_{(K)}$). However, the incubation medium for L-lysine transport was obtained by mixing 10 μl of 220 μM labeled substrate (final concentration: 20 μM) with 50 μl of 110 mM D-mannitol, 110 μM $MgSO_4$, 11 mM Tris-Hepes (pH 7.5), and 270 mM NaCl ($V_{(Na)}$) or 440 mM D-mannitol. The diffusional component (V_D) was determined by measuring the total influx of labeled substrate in the presence of 30 mM unlabeled substrate. The incubation time for transport measurements was 5 s. Values are expressed as mean ± S.D. for three experiments. Na^+-dep., $V_{(Na)} - V_{(K)}$; Na^+-indep., $V_{(K)} - V_D$.

	Transport (pmol/mg protein per 5 s)			
	control		hyperglycemia	
	Na^+-dep.	Na^+-indep.	Na^+-dep.	Na^+-indep.
Glc	13.5 ± 2.3	3.3 ± 1.6	8.6 ± 1.1	3.5 ± 0.6
Pro	102 ± 8.8	6.3 ± 2.1	133 ± 9.8	7.4 ± 1.5
Gly	2.1 ± 0.4	0.4 ± 0.3	3.1 ± 0.3	0.5 ± 0.3
Ala	13.4 ± 1.8	1.9 ± 0.4	18.2 ± 1.5	2.0 ± 0.6
Phe	13.3 ± 2.1	5.5 ± 1.7	18.1 ± 3.1	5.7 ± 1.8
Leu	29.8 ± 1.3	10.4 ± 1.8	42.6 ± 1.6	11.1 ± 1.7
Asp	0.4 ± 0.4	5.5 ± 1.3	0.5 ± 0.5	6.4 ± 1.2
Lys	0	25.3 ± 4.5	0	29.7 ± 3.4

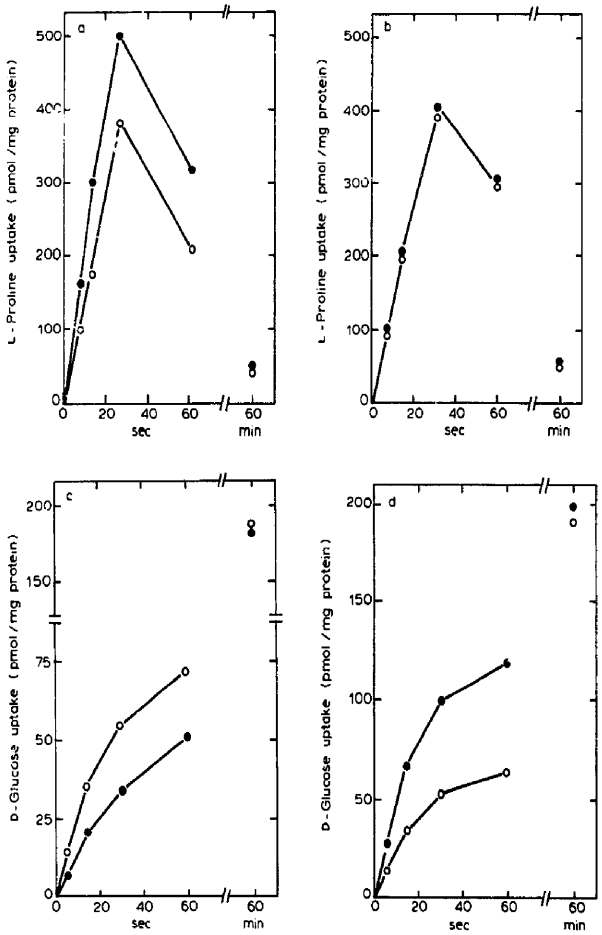

Fig. 1. Time-courses of Na^+-dependent L-proline and D-glucose transport in intestinal brush-border membrane vesicles. Membrane vesicles were prepared from control (○) and hyperglycemic (●) guinea-pigs, day 3 (a, c) and day 10 (b, d) after STZ injection. Na^+-dependent L-proline transport (a, b) and D-glucose transport (c, d) were measured with time, under the conditions described in the text and the legend of Table III. The membrane suspension and incubation medium were preincubated at 25°C for 5 min before mixing, followed by further incubation at 25°C. Each point is the mean of triplicate measurements.

(Table V) after STZ injection were comparable to the day 10 measurements (Table IV).

Time-courses of L-proline and D-glucose transport

Figs. 1a–d show the time-courses of L-proline and D-glucose transport into brush-border membrane vesicles prepared from control and hyperglycemic guinea-pig small intestine. Na^+-dependent L-proline transport in the hyperglycemic vesicles prepared day 3 after STZ injection was 30% higher than that in the control vesicles, in both the control and hyperglycemic conditions, the transport of L-proline showed a typical overshoot in the presence of a Na^+ gradient from outside to inside (Fig. 1a). In the hyperglycemic vesicles prepared day 10 after STZ injection, throughout the time-course, Na^+-dependent L-proline transport was the same as that in the control vesicles (Fig. 1b), supporting the result shown in Table IV. Na^+-dependent D-glucose transport in the hyperglycemic group day 3 after STZ injection was lower than in the control group (Fig. 1c). Na^+-dependent D-glucose transport in the hyperglycemic group day 10 after STZ injection was approximately twice as high as the control (Fig. 1d). The transport of all the substrates used reached an equilibrium at approximately the same level for both hyperglycemic and control vesicles 60 min after incubation, indicating no difference in the size of membrane vesicles of both types.

TABLE IV

L-Amino acid and D-glucose transport into brush-border membrane vesicles prepared day 10 after STZ injection

The initial transport rate was measured under the same conditions as those described in the text and the legend of Table III, except for the use of membrane vesicles prepared day 10 after STZ injection. Values are expressed as mean ± S.D. for three experiments.

	Transport (pmol/mg protein per 5 s)			
	control		hyperglycemia	
	Na^+-dep.	Na^+-indep.	Na^+-dep.	Na^+-indep.
Glc	12.3 ± 2.5	5.8 ± 1.6	21.8 ± 4.6	5.9 ± 0.5
Pro	116 ± 7.6	6.6 ± 1.8	119 ± 13.4	6.8 ± 2.6
Gly	2.1 ± 1.1	0.1 ± 0.1	2.3 ± 1.5	0.1 ± 0.1
Ala	13.5 ± 0.6	2.2 ± 0.3	14.4 ± 1.0	2.3 ± 0.8
Phe	22.8 ± 1.0	6.7 ± 0.8	21.3 ± 2.5	6.3 ± 1.9
Leu	32.1 ± 9.3	8.5 ± 1.9	29.2 ± 8.7	8.7 ± 1.1
Asp	0	8.8 ± 1.1	0	9.0 ± 0.6
Lys	0	34.5 ± 2.9	0	32.1 ± 3.5

TABLE V

L-Amino acid and D-glucose transport into brush-border membrane vesicles prepared day 21 after STZ injection

The initial transport rate was measured under the same conditions as those described in the text and the legend of Table III, except for the use of membrane vesicles prepared day 21 after STZ injection. Values are expressed as mean ± S.D. for three experiments.

	Transport (pmol/mg protein per 5 s)			
	control		hyperglycemia	
	Na^+-dep.	Na^+-indep.	Na^+-dep.	Na^+-indep.
Glc	11.3 ± 0.9	5.6 ± 0.9	21.4 ± 2.9	8.2 ± 1.4
Pro	96.6 ± 5.7	12.8 ± 2.2	96.7 ± 6.8	8.1 ± 1.3
Gly	2.5 ± 0.3	0	2.2 ± 0.2	0
Ala	15.5 ± 1.7	1.1 ± 0.1	14.0 ± 1.8	1.0 ± 0.1
Phe	24.9 ± 1.9	3.4 ± 0.3	21.9 ± 2.8	4.4 ± 1.0
Leu	37.4 ± 3.5	12.1 ± 2.2	34.0 ± 2.0	8.6 ± 1.0
Asp	0.5 ± 0.5	6.9 ± 2.1	0.5 ± 0.6	6.2 ± 1.4
Lys	0	21.6 ± 1.2	0	23.4 ± 1.3

Kinetic studies of Na^+-dependent transport of L-amino acid and D-glucose

To assess whether alterations in L-amino acid and D-glucose transport observed in the hyperglycemic guinea-pig can be attributed to changes in maximal transport capacity (V_{max}) or in carrier affinity (K_m), transport kinetics were determined (Table VI). The hyperglycemic vesicles prepared day 3 after STZ injection showed a significant increase in V_{max} values for L-proline and L-alanine transport with a concomitant significant decrease in the V_{max} value for D-glucose transport compared with the control. In the vesicles prepared day 10 after STZ injection, V_{max} for L-proline transport in the hyperglycemic group had recovered to the control level, whereas V_{max} for D-glucose transport in the same vesicles was twice as high as the control. However, the apparent K_m values for L-proline, L-alanine, and D-glucose transport on day 3 and day 10 after STZ injection remained unchanged in both the control and hyperglycemic groups. Glycine, L-phenylalanine, and L-leucine transport in vesicles prepared either day 3 or day 10 after induction of hyperglycemia showed the same changes in kinetic parameters as L-proline transport (data not shown).

Discussion

It is important to explore the mechanism of transport of nutrients across the brush-border membrane of intestinal epithelial cells, since this is the first step in absorption of nutrients. This study investigated the effect of STZ-induced hyperglycemia on L-amino acid and D-glucose transport across guinea-pig intestinal brush-border membrane. The brush-border membrane vesicles of guinea-pig intestine are highly purified as previously reported [5]. Since all vesicles prepared from the control and hyperglycemic showed a similar specific activity of alkaline phosphatase indicating a similar purity of the membrane vesicles (Table II), the results

TABLE VI

Kinetic constants for Na^+-dependent transport of L-proline, L-alanine, and D-glucose

Transport over a 5 s period was measured under the same conditions as those described in the text and the legend of Table III. Transport kinetic parameters derived from Eadie-Hofstee plots of Na^+-dependent transport in membrane vesicles of control and hyperglycemic (day 3 and day 10) guinea-pigs varying substrate concentrations from 10 μM to 5 mM. Values are expressed as mean ± S.D. for three experiments.

	K_m (μM)		V_{max} (pmol/mg protein per 5 s)	
	control	hyperglycemia	control	hyperglycemia
Day 3				
D-Glucose	238 ± 14.1	232 ± 9.2	83 ± 5.3	46 ± 3.1
L-Proline	108 ± 19.1	110 ± 14.3	610 ± 45.8	836 ± 40.3
L-Alanine	630 ± 23.9	640 ± 28.6	663 ± 80.1	960 ± 53.3
Day 10				
D-Glucose	202 ± 11.7	217 ± 14.8	87 ± 9.6	154 ± 23.3
L-Proline	96 ± 12.4	93 ± 7.4	652 ± 21.0	629 ± 26.1

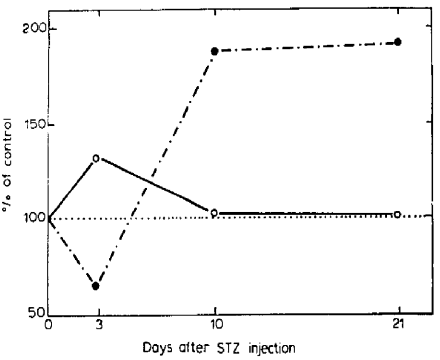

Fig. 2. Time-dependent changes in Na^+-dependent L-amino acid and D-glucose transport in intestinal brush-border membrane vesicles after STZ injection. The data summarized in the figure are from Tables III–V. ○, Na^+-dependent L-amino acid transport; ●, Na^+-dependent D-glucose transport.

summarized in Fig. 2, give the first evidence for time-dependent reciprocal changes in amino acid and glucose transport.

Ferraris et al. [20] reported that the gradient in specific binding of phloridzin along the intestinal membrane paralleled the gradient in V_{max} of glucose transport. Maenz et al. [21] discussed that an increased V_{max} showed to be mediated through an increase in the number of the transporter of glucose in the brush-border membrane vesicles and basolateral membrane vesicles of rat small intestine. Yasuda et al. [22] showed that a changed V_{max} was likely to be due to the changes in the number of the glucose transporter in renal brush-border membrane vesicles. Voorhis et al. [10] discussed that an increased V_{max} appeared to be mediated through an increase in the number of the transport carriers of glutamine in rat intestinal brush-border membrane vesicles. In our study, the changes in transport activities are attributed to the changes in the number of carriers but not to their affinity (Table VI).

The phenomenon of an increase in intestinal amino acid transport with a reciprocal decrease in glucose transport on day 3 (Fig. 2) may reflect cellular metabolic demands. The reason why the number of glucose carriers was reduced during the early phase of hyperglycemia induced by STZ injection is unclear, however, a high concentration of blood glucose may regulate transport activity. This hypothesis is supported by the fact that in renal brush-border membrane vesicles of diabetic rats, reduced Na^+-dependent glucose transport returned to the control level with lowering of the blood glucose concentration by either insulin administration or starvation [20]. Starvation altered the transport activities of rat intestinal loop, with increased amino acid transport after day 4 [21], and the reduced glucose transport after day 1 [22]. These results, together with the data shown in Fig. 2, may reflect compensation of the decrease in intestinal glucose transport by the increase in amino acid transport, so that intracellular metabolic demands are satisfied during the early phase of hyperglycemia.

The return of the increased amino acid transport to normal was accompanied by increased glucose transport after 10 days following the STZ injection (Fig. 2). That is, when hyperglycemia is prolonged, this reciprocal regulation of amino acid and glucose transport no longer occurs in the small intestinal brush-border membrane of guinea-pig. This is probably due to a compensatory effect of cellular metabolic regulation on the activity of these transport mechanisms.

The increase in amino acid transport in intestinal everted sacs [9] or brush-border membrane vesicles [10] of rats on day 5 after STZ or alloxan injection, and also the increase in glucose transport in intestinal segments of rats [11–14] day 4–8 after the injection may both reflect the transport activities at various times after the induction of hyperglycemia. The difference in reported data [9–15] and the data of this paper may be due to the use of different species of animals.

The aim of this study was to determine the changes in regulation of different amino acid transport systems [5] in guinea-pigs made hyperglycemic by STZ injection. There was no apparent difference in the increase which occurred in three Na^+-dependent amino acid transport systems day 3 after STZ injection. This is probably due to nonspecific distribution of the amino acids to the three Na^+-dependent transport systems [5], independent of their glucogenic or ketogenic properties. The three Na^+-independent amino acid transport systems were not altered by STZ injection (Tables III–V).

Carrier-mediated glucose transport across the small intestinal basolateral membrane has been shown to be increased in diabetic rats compared with controls [23,24]. The time-course of changes in amino acid and glucose transport in basolateral membrane vesicles of hyperglycemic guinea-pig small intestine remains to be determined.

This study appears to provide important information regarding nutrient absorption, since alteration in intestinal function is known to be associated with hyperglycemia and diabetes mellitus. It is therefore interesting that diabetic treatment programs involving dietary measures designed to retard intestinal glucose absorption have been considered [7].

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