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Rapid enhancement of brush border glucose uptake after exposure of rat jejunal mucosa to glucose

P A Sharp, E S Debnam, S K S Srai

Abstract

***Background*—Increased jejunal glucose transport after ingestion of carbohydrate rich diets may reflect higher concentrations of lumenal glucose. Normal processing of carbohydrate causes wide fluctuations in glucose concentration in the jejunal lumen and this raises the question of whether the high lumenal concentrations seen at peak digestion affect glucose uptake.**

***Aims*—To study the effects of 30 minute exposure of rat jejunal mucosa to glucose on sodium-glucose transporter (SGLT1) mediated glucose transport across the brush border membrane.**

***Methods*—Jejunal mucosa was exposed in vitro or in vivo to 25 mM glucose or 25 mM mannitol for 30 minutes. In addition, isolated villus enterocytes were incubated with mannitol or glucose for the same time. Brush border membrane vesicles were isolated from these preparations and phlorizin sensitive ^{3}H-D-glucose accumulation was measured.**

***Results*—Lumenal glucose in vivo significantly enhanced SGLT1 mediated glucose uptake by 49·2–57·2%. For jejunal loops in vitro, the increase was 32·0–85·2%. Kinetic analysis disclosed a 50% greater V_{max} for glucose uptake in each preparation. The facilitated and passive components of uptake were, however, unaffected by prior exposure to glucose. Incubation of villus enterocytes with 25 mM glucose did not influence glucose uptake by brush border membranes. Finally, exposure of intact mucosa to 25 mM galactose, a non-metabolised sugar also transported by SGLT1, did not alter glucose transport.**

***Conclusions*—Lumenal glucose promotes glucose transport by brush border membrane within 30 minutes. An intact mucosa is necessary for upregulation and evidence suggests that the response is mediated by locally acting mechanisms.**

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Keywords: jejunum, glucose uptake, intestinal adaptation, brush border, sodium-glucose transporter.

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Lumenal carbohydrate has profound effects on the digestive and absorptive functions of the small intestine. In particular, the feeding of a high carbohydrate diet for several days stimulates intestinal glucose uptake[1 2] and increases the expression of sodium-glucose transporter (SGLT1) at the brush border membrane.[3] The jejunal brush border membrane displays a greater response than the ileum[1] suggesting that the signal for the upregulated transport may be local, the simplest explanation being an increased concentration of lumenal carbohydrate resulting from the dietary change. Results using other models of intestinal adaptation also imply that raised lumenal sugar concentrations enhance SGLT1 expression.[4–6] Feeding a carbohydrate rich diet also promotes hexose transport at the basolateral membrane[7] and increases the concentration of enterocyte GLUT2 mRNA.[3] Comparison of the speed for adaptation of sugar transport at the basolateral membrane and brush border membrane in dietary studies suggested that basolateral changes precede those at the brush border.[7] Exposure of the jejunal mucosal surface to increased concentrations of glucose for shorter periods of time (four to eight hours) also increases jejunal glucose uptake.[8 9] Adaptation over this time scale is important in that it implies alterations in sugar transport during the intestinal processing of a meal when rapid changes in the concentration of lumenal sugar are occurring. To examine the possible mechanisms involved in the transport response to lumenal glucose, we have compared the kinetics of phlorizin sensitive (SGLT1 mediated) glucose transport following 30 minutes of exposure of either intact jejunal mucosa or isolated villus enterocytes to sugar. Glucose uptake by the brush border was measured using purified membrane vesicles prepared from jejunal mucosa or isolated enterocytes as appropriate. Preliminary reports of part of this work have been published.[10 11]

Materials and Methods

ANIMALS

Male Sprague Dawley rats (body weight 240–260 g) were used and allowed ad libitum access to water and food (No 1 expanded diet, SDS Ltd) up to the time of experimentation.

IN VIVO JEJUNAL PREPARATION

Rats were anaesthetised with an intraperitoneal injection of pentobarbitone sodium (90 mg/kg, Sagatal, May and Baker, Dagenham, UK) and a 20 cm section of jejunum, beginning 10 cm from the ligament of Treitz was selected and cannulated at either end. The contents of the loop were emptied by flushing with warm phosphate buffered saline (PBS), and mannitol

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(25 mM), or glucose (25 mM), or galactose (25 mM) dissolved in PBS was placed in the lumen avoiding distension. Ligatures were tied at either end and the segment was gently put back into the abdomen and animal body temperature was maintained at 37°C. After 30 minutes the loop was removed from the animal, opened longitudinally, and the mucosa scraped away from the underlying muscle layers. The scrapings were suspended in a homogenisation buffer containing 50 mM mannitol, 2 mM hydroxyethylpiperazime-ethanesulphonic acid (HEPES), 0·5 mM PMSF, and 100 units/ml aprotinin (pH 7·1, 15 ml buffer/mg mucosa).

ISOLATED JEJUNAL LOOPS

A 40 cm section of jejunum, starting 10 cm distal to the ligament of Trietz, was removed from anaesthetised rats and divided into two equal lengths. These were then everted to allow exposure of the mucosa to buffer. After tying a ligature at one end, the segment was filled with PBS, taking care not to overdistend the tissue, and then tied at the other end. One loop was incubated in oxygenated PBS containing 0·5 mM β-hydroxybutyrate and 1 mg/ml bovine serum albumin and either 25 mM glucose or galactose. The second loop was incubated in PBS containing 25 mM mannitol. Incubations were carried out at 37°C in a shaking water bath (100 oscillations/min). After 30 minutes the loops were removed and the mucosa removed and treated as above.

ISOLATED ENTEROCYTES

Jejunal enterocytes from the upper and mid-villus region were harvested by a calcium chelation technique.[12] Cells were incubated with oxygenated phosphate buffer containing mannitol or glucose for 30 minutes at 37°C in a shaking water bath. At the end of the incubation, cells were pelleted by centrifugation and resuspended in the homogenisation buffer (3:1 v/v buffer/cells).

BRUSH BORDER MEMBRANE VESICLES

Vesicles were prepared by a previously described method[13] with some modifications. Briefly, mucosal scrapings or upper villus enterocytes were homogenised for 2×30 seconds with an Ultra Turrax homogeniser (Janke and Kunkel, FRG) at full speed. The homogenate was centrifuged at 2500 *g* for 15 minutes. The supernatant was removed and further centrifuged at 20 500 *g* for 20 minutes. This step produces a double precipitate consisting of a white fluffy upper pellet and a hard brown lower pellet. The upper layer was removed by gentle swirling following the addition of 5 ml of a resuspension buffer containing 300 mM mannitol, 20 mM HEPES, 0·1 mM $MgSO_4$, 0·5 mM PMSF, and 100 units/ml aprotinin. The hard brown pellet was resuspended in resuspension buffer by homogenisation in a hand held homogeniser. The homogenate was diluted to a final volume of 60 ml with the same buffer and $MgCl_2$ (final concentration 10 mM) and stirred on ice for 20 minutes. Following centrifugation at 3000 *g* for 10 minutes, the supernatant was centrifuged for a further 30 minutes at 27 000 *g* to obtain the brush border pellet. All the above steps were performed at 4°C. For some experiments, brush border membrane vesicles were prepared by a similar method.[14] Glucose uptake was found to be identical for the two methods of vesicle preparation. The activities of sucrase and alkaline phosphatase in the initial homogenate and brush border membrane suspensions were determined[15,16] together with Na^+,K^+-ATPase activity[17] to calculate enzyme enrichment values in the membrane preparations.

VESICLE GLUCOSE UPTAKE

[^{3}H]-D-Glucose transport (11–470 or 970 μM) used freshly prepared brush border membrane vesicles as described previously.[18] Uptake measurements were carried out at t=4 s and therefore represent initial unidirectional uptake. To determine the phlorizin sensitive (SGLT1 mediated) component of uptake, parallel experiments measured uptake of D-glucose in presence of phlorizin (1 mM), a concentration which inhibits electrogenic glucose uptake at concentrations up to 32 mM.[19] These data were subtracted from uptake in absence of the blocker. V_{max} (maximum transport capacity) and K_t (glucose concentration at half V_{max}) for SGLT1 mediated glucose transport were derived using a non-linear least squares curve fitting program (Microcal Origin).

In rat intestine, glucose may utilise the brush border fructose transporter, GLUT5 and moreover, expression of the facilitated sugar transporter GLUT2 may ocur at the brush border membrane. These findings, and others, imply pathways for glucose movement at the brush border membrane in addition to that occurring via SGLT1.[5,20] For this reason, additional uptake experiments were performed using 20 mM glucose, a concentration in keeping with the low affinity of facilitated sugar transporters for glucose. At 20 mM glucose it was, however, necessary to separate phlorizin insensitive glucose movement into its facilitated and passive components, a procedure which is unnecessary at concentrations below 1 mM. Passive transport was taken as the uptake of 20 mM L-glucose. Subtraction of L-glucose transport from phlorizin-insensitive D-glucose uptake allowed the facilitated component of glucose uptake to be quantified.

STATISTICS

All results are means (SEM). Differences between means were evaluated by Student's *t* test, paired or unpaired as appropriate, and considered significant at $p<0·05$.

CHEMICALS

Radioisotopes were obtained from Amersham International (Amersham, UK). All other

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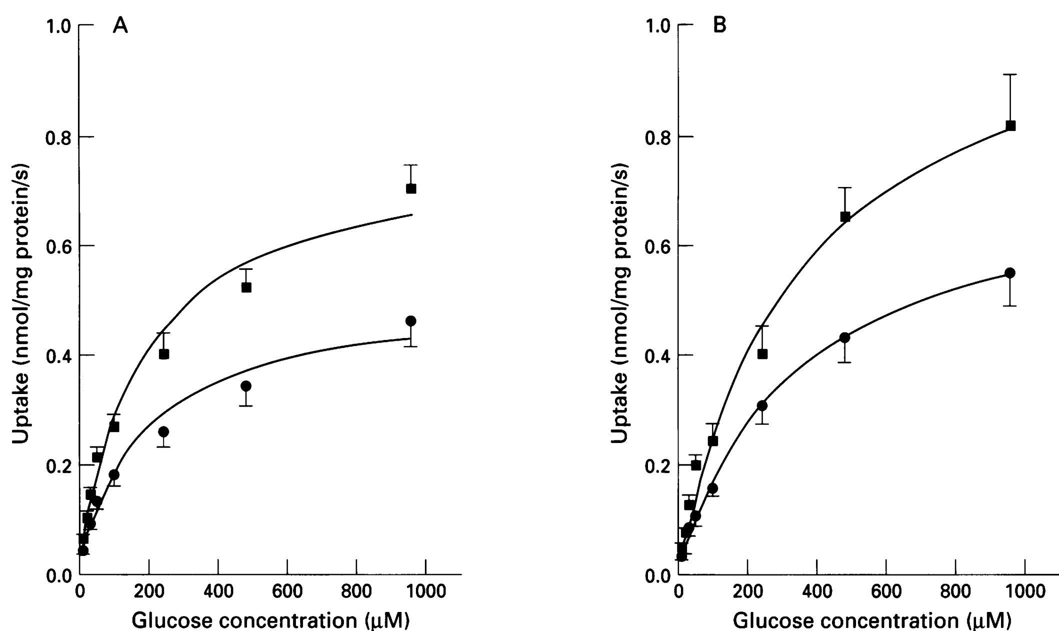

Figure 1: Effects of 30 minute incubation of jejunal loops in vivo (A) or isolated jejunum (B) with buffer containing 25 mM glucose (■) or 25 mM mannitol (●) on glucose uptake by brush border membrane prepared from this tissue. Results have been corrected for phlorizin insensitive uptake and therefore represent SGLT1 mediated transport. Values are means(SEM) of six to 11 experiments in each group.

chemicals were of analytical grade and were obtained from either Sigma (Poole, Dorset, UK) or Merck Ltd (Poole, Dorset, UK).

Results

PURITY OF MEMBRANE VESICLES

Vesicles from brush border membrane, prepared from either whole mucosa or villus enterocytes, were enriched 16 to 18-fold for sucrase and 10 to 13-fold for alkaline phosphatase but not for Na^+, K^+- ATPase compared to the homogenate. Vesicles displayed the expected overshoot for phlorizin sensitive D-glucose uptake (results not shown).

MUCOSAL EXPOSURE TO GLUCOSE

Phlorizin sensitive glucose uptake using vesicles prepared from in vivo loops exposed to glucose containing PBS was 49·2–57·2% higher than that using membrane prepared from loops exposed to 25 mM mannitol (Fig 1A). The increases seen were significant over the entire concentration range of glucose used. Incubation of paired sections of isolated intestine with glucose also promoted glucose transport by between 32·0 and 85·2% (p<0·001 to <0·05 by paired *t* test, Fig 1B). Kinetic analysis of glucose uptake disclosed a significantly higher V_{max} (+50·0% both in vitro and in vivo) but unchanged K_t of the transport process (Table I). Further experiments were carried out to show whether the brush border membrane transport response was specific for glucose in the incubation buffer. Galactose was used as this hexose is also handled by SGLT1 but not metabolised by enterocytes. Mucosal exposure to galactose both in vivo and in vitro was without effect on brush border membrane glucose uptake (Figs 2A and 2B; Table).

The effect of mucosal glucose exposure on phlorizin insensitive carrier mediated glucose transport was also assessed. These experiments used a sugar concentration of 20 mM as the K_t for facilitated glucose transport is considerably higher than that for SGLT1 dependent movement. L-glucose uptake was also determined to correct for passive transport. Glucose exposure in vivo was found to be without effect on both facilitated (mannitol: 0·716 (0·116) (n=7), glucose: 0·722 (0·130) (n=7) nmol/mg protein/4s, p>0·05) and passive glucose uptake (mannitol: 0·207 (0.041) (n=7), glucose: 0·185 (0·036) (n=7) nmol/mg protein/4s, p>0·05).

ISOLATED ENTEROCYTES

Isolated villus enterocytes were incubated with 25 mM glucose for the same period of time as

Kinetic variables of K_t and V_{max} for phlorizin sensitive glucose accumulation by brush border membrane vesicles prepared from in vivo jejunal loops or everted jejunum exposed to 25 mM mannitol, 25 mM galactose or 25 mM glucose for 30 minutes, or isolated villus cells exposed to 25 mM mannitol glucose or 25 mM glucose for 30 minutes

Condition	*K_t (μM)*	*V_{max} (nmol/mg protein/s)*
In vivo exposure to:		
Glucose:		
Mannitol control	193·5 (41·4)	0·52 (0·04)
Glucose	188·2 (39·7)	0·78 (0·06)*
Galactose:		
Mannitol control	191·0 (37·0)	0·56 (0·04)
Galactose	182·7 (30·6)	0·64 (0·04)
In vitro exposure to:		
Glucose:		
Mannitol control	344·6 (32·3)	0·74 (0·03)
Glucose	355·5 (67·9)	1·11 (0.09)*
Galactose:		
Mannitol control	243·6 (22·3)	1·05 (0·05)
Galactose	205·5 (36·5)	0·93 (0·07)
Exposure of isolated cells to:		
Mannitol	231·1 (33·2)	1·35 (0·09)
Glucose	233·5 (21·1)	1·27 (0·05

Values are means (SEM) (n=5–11 preparations/group).
*p<0·05 *v* mannitol control.

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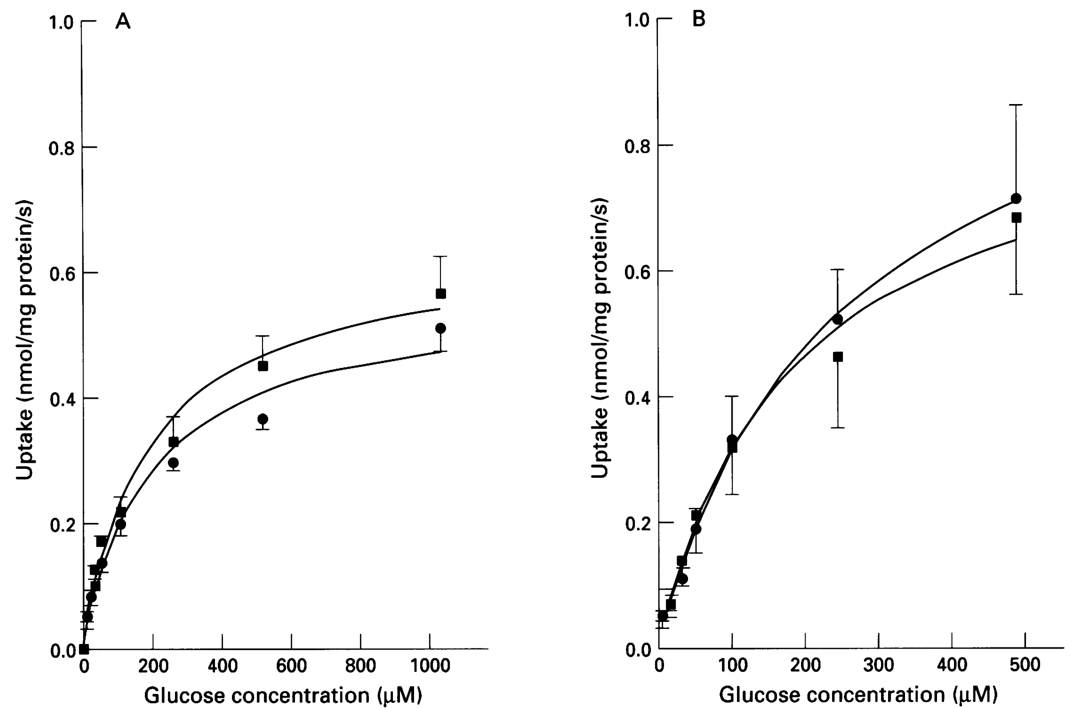

Figure 2: Effect of 30 minute incubation of jejunal loops in vivo (A) or isolated jejunum (B) with PBS containing 25 mM galactose (■) or 25 mM mannitol (●) on glucose uptake by vesicles of brush border membrane prepared from this tissue. Results have been corrected for phlorizin insensitive uptake and therefore represent SGLT1 mediated transport. Data are means (SEM) of six experiments in each group.

intact epithelium. We have previously shown that cells obtained using the Ca^{2+} chelation procedure retain their structure, exclude trypan blue up to 60 minutes after isolation,[12] actively accumulate sugar,[12] and exhibit increased sugar transport after their exposure to peptide hormones.[18 21] These findings imply that enterocytes retain their structural and functional viability during their isolation and the subsequent 30 minute incubation period. By contrast with the situation with intact jejunum in vivo and in vitro, glucose uptake

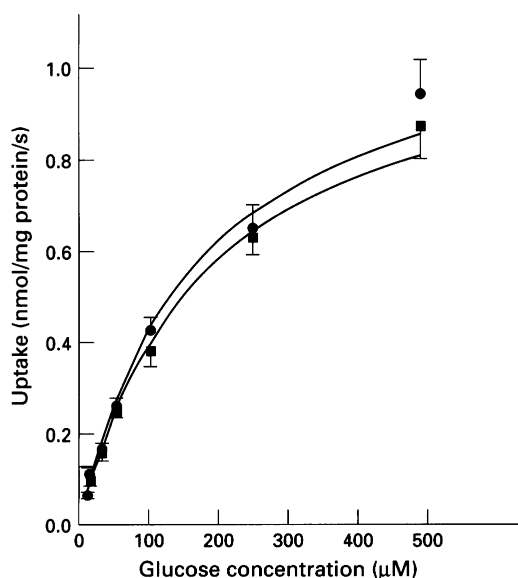

Figure 3: Effects of 30 minute exposure of isolated enterocytes to 25mM glucose (■) or 25 mM mannitol (●) on glucose accumulation by brush border membrane vesicles prepared from these cells. Results have been corrected for phlorizin insensitive uptake and therefore represent SGLT1 mediated transport. Data are means (SEM) of five experiments in each group.

after enterocyte exposure to glucose was not different to that seen using 25 mM mannitol (Fig 3, $p>0\cdot1$ at all concentrations; Table).

Discussion

Previous studies have shown that increased dietary carbohydrate promotes glucose uptake by brush border membrane,[1 2] the likely explanation being that raised concentrations of lumenal sugar increase the expression of the SGLT1 transporter.[3–5 7] An enhanced basolateral glucose transport has also been noted after increased carbohydrate ingestion[7] and this may be a consequence of increased expression of GLUT2.[3] The findings of upregulation of glucose transport four to eight hours after in vivo exposure of the jejunal mucosa to glucose[8 9] indicates that adaptation to lumenal carbohydrate occurs more rapidly than the time required for epithelial replacement, and implies that changes in sugar uptake are not necessarily initiated at crypt level but can take place during the migration of cells along the villus. Confirmation of this notion has come from this present study, in which exposure of intact jejunal mucosa to glucose for only 30 minutes was seen to enhance SGLT1 mediated glucose transport.

The mechanism for this very rapid adaptation of sugar transport by brush border membrane is unclear. The unaltered facilitated glucose uptake implies a transporter specificity in the response of the brush border membrane to glucose whereas the rapid onset makes it unlikely that new protein synthesis is taking place. Failure to detect upregulation of glucose uptake by the brush border membrane after exposure of viable, isolated cells to glucose implies an explanation other than increased

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enterocyte metabolism. An alteration in the rate of insertion of SGLT1 transporters into the membrane, or greater stabilisation of the protein can also be ruled out as enhanced phlorizin binding is only detectable 12 to 24 hours after switching to a high carbohydrate diet.[22] The recent finding that an SGLT1 regulatory protein is necessary for full functional expression of this transporter[23] makes it possible that lumenal glucose may act by regulating the activity of existing membrane associated SGLT1. It is known that transport adaptation may result from recruitment of normally non-transporting regions of the villus.[12 18] Lumenal glucose could enhance transport in this way or alternatively may influence the uptake capacity of mature enterocytes at the upper villus.

We have previously shown that the potential difference across the brush border membrane is subject to physiological control, hyperpolarisation having been noted in many experimental conditions.[14 23-26] Because the potential difference is a driving force for SGLT1 mediated glucose transport,[24] it is possible that an increased electrochemical gradient across the brush border membrane, generated by mechanisms operating at subepithelial level in response to lumenal glucose, may contribute to our present findings.

The absence of rapid adaptation after incubation of isolated enterocytes with glucose indicates that an intact mucosa is required for the response. Furthermore, the stimulation of glucose uptake by brush border membrane when isolated intestine was exposed to lumenal glucose is strong support for local nervous or paracrine mediation. The failure of galactose, a hexose which also utilises SGLT1, to upregulate glucose transport, implies that glucose does not have to be absorbed into enterocytes, and that there is a substrate specificity for rapid lumenal upregulation of transport. Taken together, our data suggest that mucosal chemoreceptors respond specifically to glucose and initiate a reflex which culminates in enhanced local glucose transport. It is of interest that myenteric nerves have recently been implicated in the altered epithelial ion secretion induced by lumenal glucose.[27] Possible paracrine candidates for the responses shown in this present study include bradykinin and prostaglandins, which promote glucose transport across the jejunal brush border membrane.[21 28] Both bradykinin and prostaglandins alter K^+ conductance in polarised epithelial cells,[29 30] and this would be expected to modify potential difference across the brush border membrane. Finally, mucosal exposure to glucose stimulates the release of neurotensin[31] and it is possible that this neurotransmitter may also modulate glucose uptake locally.

The relevance of our findings regarding control of glucose absorption needs to be considered. Lumenal concentrations of glucose fluctuate greatly during carbohydrate digestion and absorption[5 32] and our findings suggest that the capacity for intestinal glucose uptake is not fixed but is constantly adapting in response to prevailing lumenal concentrations of glucose. In this way, rapid mucosal adaptation to glucose might be important for the coupling of glucose transport to its lumenal availability during intestinal processing of carbohydrate. Additionally, raised lumenal glucose concentration in more distal areas of small intestine, may also increase glucose uptake in proximal small intestine by activating another reflex[33] in conditions where unusually high levels of sugar are present in the intestinal tract. Together, the two responses would ensure that only minimal amounts of sugar enter the colon.

In conclusion, we have demonstrated that exposure of jejunal mucosa to glucose increases glucose uptake by brush border membrane within 30 minutes by a local mechanism which requires an intact mucosa and a specificity for glucose as the signal. At the cellular level, enhanced activity of membrane associated SGLT1 or a greater electrochemical driving force across the brush border membrane are likely to be involved in the response.

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