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# Alanine Enhances Jejunal Sodium Absorption in the Presence of Glucose: Studies in Piglet Viral Diarrhea

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**ABSTRACT. We measured the response of jejunal sodium (Na) absorption to neutral amino acid (L-alanine) and to dipeptides (L-alanyl-L-alanine, glycylsarcosine) in normal piglets and in piglets with acute viral diarrhea after experimental infection with transmissible gastroenteritis (TGE) virus. In the TGE jejunum villi were blunted, crypts were deepened, and the epithelium was composed of relatively undifferentiated cells with reduced disaccharidase, decreased sodium-potassium-stimulated ATPase, and elevated thymidine kinase activities. The response of Na absorption to a maximal concentration of L-alanine (20 mM) or D-glucose (30 mM) was significantly blunted in TGE jejunum in Ussing chambers. However, the addition of L-alanine together with D-glucose caused a significantly greater increment of Na absorption than either L-alanine or D-glucose alone in control and TGE tissue. The effect of Na absorption of the dipeptide L-alanyl-L-alanine (10 mM), which was rapidly hydrolyzed by control and TGE mucosa, was similar to that of L-alanine (20 mM), while glycylsarcosine, a poorly hydrolyzed dipeptide, did not change net Na absorption in the jejunum. Our data support the concept of separate carrier systems for neutral amino acid and hexose in the crypt-type intestinal epithelium characterizing viral enteritis. We speculate that a sodium-cotransporting amino acid, if added to oral glucose-electrolyte solutions, could benefit oral rehydration therapy in acute viral diarrhea; neither of the dipeptides tested here can be expected to enhance absorption to any greater extent than its constituent amino acids. (*Pediatr Res* 20: 879–883, 1986)**

### Abbreviations

**Isc, short-circuit current**
**Na, sodium**
**$J^{Na}_{ms}$, Na flux from mucosa to serosa**
**$J^{Na}_{sm}$, Na flux from serosa to mucosa**
**$J^{Na}_{net}$, net Na flux**
**$\Delta J^{Na}_{net}$, increment in net Na flux**
**$Na^+$-$K^+$-ATPase, sodium-potassium-stimulated adenosinetriphosphatase**
**ORT, oral rehydration therapy**
**TGE, transmissible gastroenteritis**
**WHO, World Health Organization**
**3-O-MG, 3-O-methyl-D-glucose**
**Ala-Ala, L-alanyl-L-alanine**

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ORT has greatly improved the outlook for millions of babies afflicted each year with acute enteritis. The current WHO/UNICEF formulation for oral rehydration has been very effective in restoring the water and electrolyte status of patients with diarrhea, but it does not diminish stool losses (1, 2). To accelerate clinical recovery and promote general acceptance of ORT, a solution that actually reduces diarrheal volume would be very desirable.

One theoretical approach to improving standard ORT is to incorporate additional nonionic solute in its formulation to promote water and salt absorption in the diseased intestine. To evaluate the pathophysiological basis for such an approach we studied the effect of a neutral amino acid and certain dipeptides on Na flux in the small intestine during acute viral enteritis. Hellier *et al.* (3) demonstrated that certain amino acids promote small intestinal absorption in man (3). Furthermore, preliminary studies have shown a beneficial effect of an amino acid-containing oral rehydration solution in treating diarrhea (4, 5). Our current *in vitro* data provide a theoretical basis for the clinical testing of oral rehydration solutions supplemented with neutral amino acid.

## MATERIALS AND METHODS

*Animal techniques.* Two-wk-old York Landrace piglets were weaned and maintained for 3 days on evaporated cows' milk; 21 received a standard intragastric inoculum of the Purdue strain of TGE virus (6) and 28 uninfected littermates served as age-matched controls. Infected pigs were killed 40 h later by parenteral injection of 325 mg of pentobarbital Na. Although vomiting and diarrhea had developed in TGE-infected piglets, their weights (2550 ± 90 g) did not differ significantly from those of controls (2750 ± 90 g).

*Enzyme and transport studies.* Immediately after death, beginning 10 cm distal to the ligament of Treitz, the first 8 cm of jejunum was removed quickly, flushed with normal saline, and mounted in Ussing chambers. The next 25 cm was removed and flushed, the proximal 2 cm taken for light microscopy, and the mucosa scraped off the remainder with a glass slide, homogenized, and frozen at −40° C. These mucosal homogenates were assayed for total sucrase and lactase (7), $Na^+$-$K^+$-ATPase (8), and thymidine kinase (9) activities. For ion flux measurements, jejunal mucosa was stripped of muscle, opened, and mounted quickly in modified Ussing chambers (exposing an area of 1.29 $cm^2$) (9). Each side of the tissue was bathed at 37° C in 10 ml

oxygenated Krebs-Ringer bicarbonate buffer (pH 7.4) containing (mM): Na 143, potassium 10, magnesium 1.1, calcium 1.25, chloride 128, $HCO_3$ 25, $H_2PO_4$ 2, and acetate 3 as a source of energy. Jejunal tissue was mounted in the chambers within 30 min of the piglet's death and continuously short-circuited, with the short-circuit current adjusted at 10-min intervals (10). Transmucosal potential difference and conductance were stable for the 2-h study periods, indicating viability of the preparations.

$^{22}Na$ (Amersham, Montreal, Canada) was added to the mucosal or serosal chamber, and after a 15-min equilibration period, unidirectional Na fluxes based on the rate of appearance of label in the opposite chamber were calculated from 1-ml samples drawn at 10-min intervals (10, 11). After 55 min, 5 ml of Krebs buffer containing L-alanine (5, 10, 20, or 50 mM, Sigma Chemical Co., St. Louis, MO), Ala-Ala (10 mM, Sigma Chemical Co.), D-glucose (5, 30, 50 or 100 mM, BDH Chemicals, Toronto, Ontario, Canada), glycylsarcosine (5, 20, or 50 mM, Sigma Chemical Co.), L-alanine (50 mM) and D-glucose (30 mM), or L-alanine (50 mM) and 3-O-methyl-D-glucose (3-O-MG, 30 mM, Sigma Chemical Co.) was added to the mucosal and serosal chambers to maintain osmotic balance, as previously described (12). Fifteen min later, unidirectional Na fluxes again were measured at 10-min intervals for 1 h. $J^{Na}_{ms}$ and $J^{Na}_{sm}$ were determined from paired jejunal segments, and net Na flux was calculated using the formula $J^{Na}_{net} = J^{Na}_{ms} - J^{Na}_{sm}$. When conductance in paired tissues differed by more than 20%, data from the chambers were discarded.

In chambers containing control or TGE tissue, we estimated L-alanyl-L-alanine hydrolysis in the mucosal buffer using ion exchange chromatography to measure the remaining dipeptide. After a 10-min incubation the L-alanyl-L-alanine peak, separate from that for L-alanine, was compared with standards of known concentration.

*Microscopic studies.* Tissue was fixed in Bouin's solution, blocked in paraffin, and stained with hematoxylin and eosin. Using a calibrated micrometer eyepiece to measure 10 to 15 representative crypt-villus units, one observer examined all sections with light microscopy without prior identification.

*Statistics.* Data were compared statistically using Student's *t* test.

Table 1. *Mucosal structure and enzymes in piglet jejunum (mean ± SEM)*

| | Controls | TGE* |
|---|---|---|
| Structure | | |
| Villus ht (μm) | 294.6 ± 12.8 (22)† | 123.8 ± 17.1 (16) |
| Crypt depth (μm) | 134.4 ± 6.2 (22) | 189.1 ± 9.8 (16) |
| Villus/crypt ratio | 2.3 ± 0.1 (22) | 0.7 ± 0.1 (16) |
| Enzyme activities | | |
| Sucrase ($U \cdot g^{-1}$) | 55.3 ± 7.0 (28) | 2.5 ± 0.5 (21) |
| Lactase ($U \cdot g^{-1}$) | 72.9 ± 6.6 (28) | 4.5 ± 0.7 (21) |
| $Na^+$-$K^+$-ATPase ($U \cdot g^{-1}$) | 90.6 ± 6.8 (28) | 42.4 ± 8.5 (21) |
| Thymidine kinase ($pmol \cdot mg^{-1} \cdot h^{-1}$) | 9.7 ± 0.9 (28) | 42.2 ± 0.9 (21) |

* All TGE data differ significantly from control data ($p < 0.001$).
† Number of animals is given in parentheses.

## RESULTS

*Mucosal structure and enzymes (Table 1).* Compared with noninfected controls, in piglets with TGE, jejunal villi were blunted ($p < 0.001$) and crypts deepened ($p < 0.001$) with substantial acute inflammation in the lamina propria 40 h after TGE infection (Table 1). Mucosal sucrase, lactase, and $Na^+$-$K^+$-ATPase activities were diminished ($p < 0.001$), whereas the proliferative marker thymidine kinase was elevated ($p < 0.001$) in TGE tissue. These findings, consistent with our earlier observations of this disease (13), suggest that the jejunal epithelium at the 40-h acute diarrheal phase of TGE was composed of relatively undifferentiated crypt-type enterocytes.

*Effect of different concentrations of L-alanine and D-glucose on electrical properties and Na flux.* The response of Isc in control piglet jejunum to increasing concentrations of L-alanine and D-glucose is shown in Figure 1. Maximal responses (ΔIsc) were noted at 20 mM L-alanine and 30 mM D-glucose; maximal increases of net Na flux were also noted at these concentrations. In TGE jejunum, maximal response occurred at the same concentrations.

Table 2 summarizes electrical and Na flux responses to L-alanine and D-glucose in short-circuited control and TGE jejunum. Under basal conditions in the absence of L-alanine or D-glucose, unidirectional Na fluxes were reduced in TGE jejunum compared with controls; net Na flux in TGE jejunum was secretory and did not differ from that in controls. After addition of either L-alanine or D-glucose to the mucosal and serosal buffers, control jejunum responded as expected with significant increases in $J^{Na}_{ms}$ and $J^{Na}_{net}$. TGE jejunum also responded to L-alanine with increases in $J^{Na}_{ms}$ and $J^{Na}_{net}$, and to D-glucose with increases in $J^{Na}_{net}$; however, these increments were less than those observed in controls ($p < 0.01$). Addition of L-alanine or D-glucose did not alter $J^{Na}_{sm}$ in either control or TGE epithelia.

Data from experiments comparing the Na flux responses to L-alanine plus D-glucose with those to maximal concentrations of L-alanine or D-glucose alone in short-circuited jejunum are shown in Figure 2. In paired sets of chambers, response to the two substrates together exceeded the response to either L-alanine ($p < 0.01$) or D-glucose ($p < 0.05$) in control and in TGE

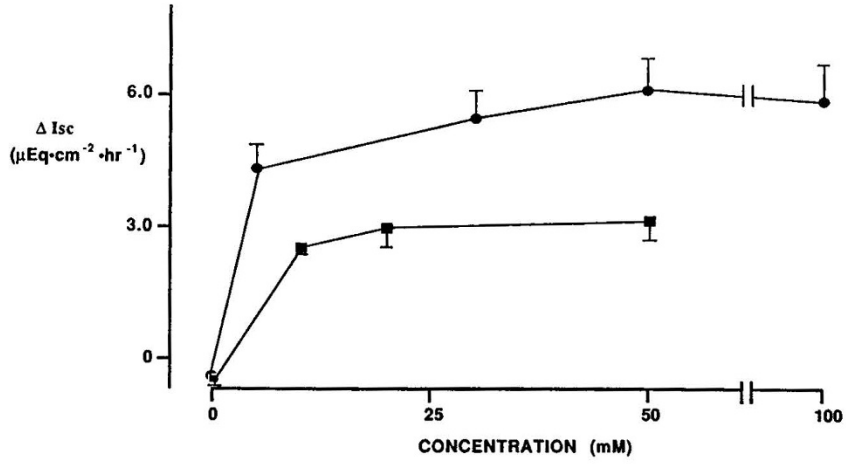


Fig. 1. Increase of ΔIsc in response to different concentrations of L-alanine (■) and D-glucose (●) in control piglet jejunum (mean ± SEM).

Table 2. *Transmucosal unidirectional ($J^{Na}_{ms}$, $J^{Na}_{sm}$) and net Na fluxes ($J^{Na}_{net}$), conductance, and Isc: response to L-alanine and D-glucose in TGE jejunum (mean ± SEM)*

| | | Na flux ($\mu$Eq·cm$^{-2}$·h$^{-1}$) | | | | Conductance (mmho·cm$^{-2}$) | Isc ($\mu$Eq·cm$^{-2}$·h$^{-1}$) |
|---|---|---|---|---|---|---|---|
| | $n$ | $J_{ms}$ | $J_{sm}$ | $J_{net}$ | $\Delta J_{net}$ | | |
| Basal | | | | | | | |
| Controls | 15 | 9.3 ± 0.7 | 10.6 ± 0.8 | −1.4 ± 0.6 | | 20.5 ± 1.2 | 2.7 ± 1.2 |
| TGE | 15 | 5.9 ± 0.2* | 7.6 ± 0.3* | −1.7 ± 0.3 | | 14.0 ± 0.5* | 1.8 ± 0.1* |
| L-Alanine (20 mM) | | | | | | | |
| Controls | 15 | 11.9 ± 1.0† | 10.8 ± 0.6 | 1.1 ± 0.7‡ | 2.5 ± 0.4 | 27.3 ± 1.4‡ | 5.8 ± 0.5‡ |
| TGE | 15 | 7.9 ± 0.5*,† | 8.5 ± 0.4* | −0.6 ± 0.4† | 1.1 ± 0.3* | 17.4 ± 0.8*,‡ | 3.6 ± 0.4*,‡ |
| Basal | | | | | | | |
| Controls | 8 | 9.5 ± 0.7 | 10.6 ± 0.4 | −1.1 ± 0.4 | | 20.3 ± 1.2 | 2.5 ± 0.1 |
| TGE | 9 | 6.8 ± 0.7* | 8.0 ± 0.7* | −1.2 ± 0.4 | | 16.6 ± 1.7 | 1.8 ± 0.1* |
| D-Glucose (30 mM) | | | | | | | |
| Controls | 8 | 14.8 ± 0.7‡ | 9.8 ± 0.5 | 5.0 ± 0.5‡ | 6.1 ± 0.7 | 28.3 ± 3.1‡ | 6.8 ± 0.8‡ |
| TGE | 9 | 8.1 ± 1.1* | 7.9 ± 0.7§ | 0.3 ± 0.4*,‡ | 1.5 ± 0.4* | 20.2 ± 2.0* | 3.8 ± 0.5*,‡ |

* $p < 0.01$ compared with controls.
† $p < 0.05$ compared with basal.
‡ $p < 0.01$ compared with basal.
§ $p < 0.05$ compared with controls.

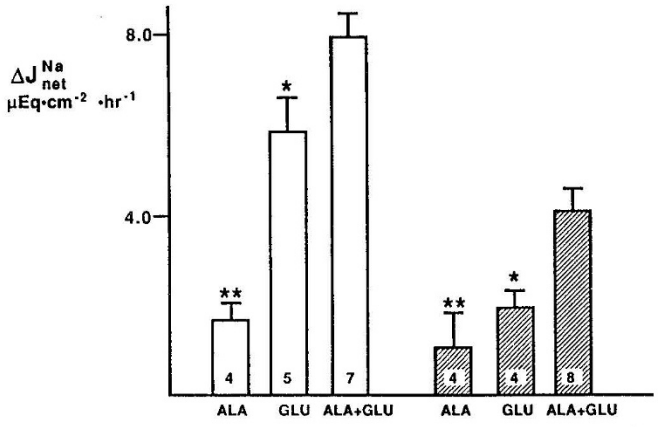


Fig. 2. Response of Na absorption in control (□) and TGE (▨) piglet jejunum after addition of L-alanine (*ALA*) (50 mM), D-glucose (*GLU*) (30 mM), and L-alanine (50 mM) with D-glucose (30 mM) (ALA + GLU). Paired observations in same epithelia. Significant differences between responses to L-alanine with D-glucose and to L-alanine or D-glucose are shown by one ($p < 0.05$) or two ($p < 0.01$) *asterisks*. Na absorptive response is significantly reduced in TGE tissue compared with controls ($p < 0.01$) when D-glucose or L-alanine with D-glucose is added. *Numerals* and *bars* indicate number of studies (mean ± SEM).

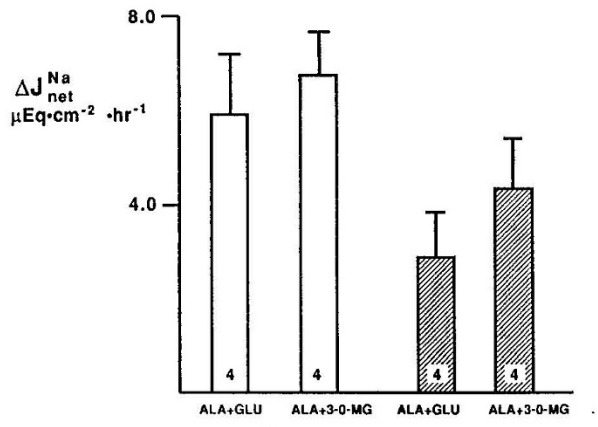


Fig. 3. Response of flux ($\Delta J^{Na}_{net}$) in control (□) and TGE (▨) piglet jejunum after addition of L-alanine and D-glucose or L-alanine and 3-O-MG. Response to L-alanine + 3-O-MG in TGE jejunum is significantly less than that of control jejunum ($p < 0.05$) (mean ± SEM).

jejunum. We compared the effect of L-alanine plus D-glucose with that of L-alanine plus the nonmetabolizable hexose 3-O-MG in control and TGE jejunum; in both study groups the $\Delta J^{Na}_{net}$ in response to L-alanine with D-glucose was the same as that to L-alanine with 3-O-MG (Fig. 3).

In control jejunum, unidirectional Na fluxes in the presence of D-glucose at 30, 50, and 100 mM were equivalent. This indicates that above the maximal concentration, an increase in osmolarity in the range tested did not significantly alter jejunal Na transport or passive flux.

Electrical responses of the tissues to L-alanine and D-glucose were in keeping with the Na transport data described above. In both groups of piglets increments in Isc were equivalent to increments in $J^{Na}_{net}$ (Fig. 1, Table 2). Isc increased significantly more after L-alanine plus D-glucose than after either alone ($p < 0.05$) in control and TGE tissue. Epithelial conductance (G), increased to the same extent ($p < 0.01$) after L-alanine or D-glucose in both control and TGE jejunum (Table 2). In the experiments summarized in Figure 2, L-alanine plus D-glucose increased conductance by 8.4 ± 2.2 mmho·cm$^{-2}$, an increment that did not differ from the increase after L-alanine (3.8 ± 1.0 mmho·cm$^{-2}$) or D-glucose (4.4 ± 1.7 mmho·cm$^{-2}$) alone.

*Effect of glycylsarcosine and Ala-Ala on Na transport.* Added to control jejunum, the synthetic dipeptide glycylsarcosine, known not to be susceptible to hydrolysis at the brush border membrane (14), increased Isc in a concentration-dependent manner at 5, 20, and 50 mM but did not affect $J^{Na}_{ms}$ or $J^{Na}_{net}$ (Fig. 4).

Control epithelium responded to Ala-Ala with an increase in net Na absorption ($p < 0.05$ compared with basal period) similar to that occurring in response to L-alanine. However, in these preparations of TGE jejunum, $J^{Na}_{net}$ did not increase significantly above basal Na flux after addition of either the amino acid or the dipeptide (Fig. 5), although $J^{Na}_{ms}$ increased ($p < 0.05$). Ion exchange chromatography of the mucosal buffer solution containing Ala-Ala after 10-min exposure to control mucosa showed complete hydrolysis of Ala-Ala ($n = 4$ chambers); in chambers containing TGE mucosa ($n = 3$), hydrolysis was 86% complete.

## DISCUSSION

Our studies have demonstrated an effect of L-alanine and D-glucose on sodium transport in control and TGE jejunum that significantly exceeded the response to maximal concentrations of either substrate alone. This additive effect might have been due to the presence of two noncompeting transport sites or to

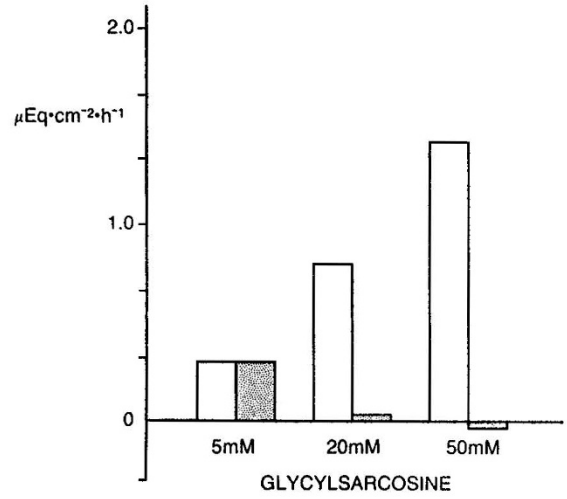


Fig. 4. Increases of Isc (□) and $J^{Na}_{net}$ (▩) in paired Ussing chambers in response to addition of different concentrations of glycylsarcosine in control piglet jejunum (mean ± SEM).

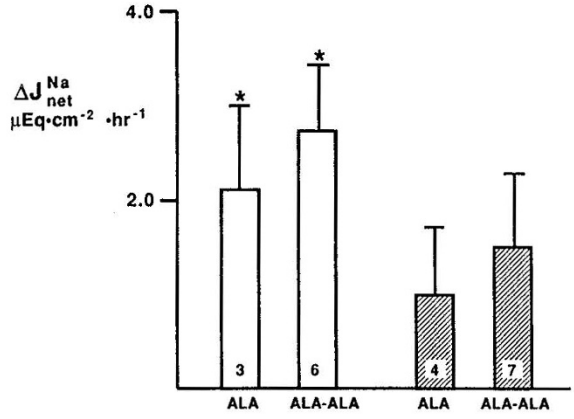


Fig. 5. Increase of Na flux ($\Delta J^{Na}_{net}$) in control (□) and TGE (▨) piglet jejunum after addition of L-alanine (*ALA*) (20 mM) or Ala-Ala (10 mM) (mean ± SEM). An *asterisk* indicates that the substrate significantly enhanced net Na absorption ( $p < 0.05$).

increased sodium transport by a single carrier due to enhanced glucose metabolism. The response to L-alanine with 3-O-MG, a nonmetabolizable hexose transported by the same carrier pathway as other hexoses but with a reduced apparent receptor affinity compared with D-glucose (15), showed that the response to D-glucose with L-alanine cannot be attributed to a nonspecific effect of D-glucose on tissue metabolism. Increments in jejunal flux after adding 3-O-MG with L-alanine did not differ from the response to D-glucose with L-alanine. Thus, our data favor the interpretation that separate carrier systems for D-glucose and L-alanine are present in the jejunum in health and during viral enteritis.

In addition, we have identified a defect in L-alanine-facilitated Na absorption during acute viral diarrhea. Control piglet jejunum responded to either L-alanine or D-glucose with significant increments in net Na absorption, as previously reported in other mammalian (16) and nonmammalian (17) species. After TGE infection, there was a significant impairment of sodium transport response to either L-alanine or D-glucose (Table 2). Previous investigations from this laboratory have shown that TGE causes a significant reduction in transjejunal D-glucose-facilitated Na absorption (9) and impairment of brush border membrane Na gradient-driven D-glucose transport (18). Therefore, our finding of a defect in a similar but distinct epithelial transport system (19–22), that of neutral amino acid-sodium cotransport, might have been anticipated in this acute enteritis. Previous studies (13) and the current enzyme and morphologic data suggest that the epithelium is composed of relatively undifferentiated crypt-type enterocytes during acute TGE diarrhea. We speculate that these crypt-like cells are defective in the Na absorptive response both to neutral amino acid and to D-glucose.

Certain dipeptides have been reported to be absorbed more efficiently than their constituent amino acids both in normal volunteers (25) and in patients with celiac disease (24, 25). Dipeptides do not compete with amino acids for mucosal uptake (23) and they have been found to increase Na absorption in man (3). Because transport of a poorly hydrolyzed dipeptide, glycylsarcosine, into hamster intestinal rings was reduced by metabolic inhibitors and by replacement of mucosal Na with potassium (14), dipeptides were thought to be cotransported with Na (23). However, evidence is accumulating that "uphill" Na-driven transport of dipeptides may not occur in the brush border of small intestine (26–28). Probably the effect of Ala-Ala on sodium transport in our studies resembled that of L-alanine because the dipeptide was hydrolyzed rapidly at the brush border surface of both control and TGE tissue. The failure of Na transport to respond to glycylsarcosine in control jejunum further supports the emerging concept that Na gradient-dependent dipeptide transport may not occur. The observed concentration-dependent increase in transmucosal Isc in response to glycylsarcosine, indicating stimulation of electrogenic transport in the absence of a change in Na flux, might be attributable to a recently postulated dipeptide-$H^+$ cotransport mechanism in intestinal brush border (28, 29).

That the relatively poorly differentiated epithelium characterizing viral enteritis responds better to glucose combined with an amino acid than to either of these substrates alone could have implications for the oral treatment of viral diarrhea. The ORS now advocated by WHO is much more effective than earlier traditional treatments for children with acute enteritis (1, 2, 30–32). Nevertheless, between 7 and 15% of children treated with ORS for dehydration resulting from viral diarrhea receive intravenous therapy, often because stool losses continue to exceed oral fluid intake (1, 31, 32). Our data support the clinical evaluation of an appropriate amino acid in an oral rehydration solution to improve Na and water absorption. Several clinical trials have shown that modestly hypertonic oral treatment solutions containing amino acid may reduce stool output as well as oral fluid requirements in patients with acute diarrhea (4, 5, 33). However, based on our limited experiments, the addition of dipeptides to an oral treatment solution would not be expected to confer an absorptive advantage over amino acids.

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