Jejunal and Ileal Glucose-Stimulated Water and Sodium Absorption in Tropical Enteropathy: Implications for Oral Rehydration Therapy

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Key Words: Jejunal, ileal absorption • Tropical enteropathy • Oral rehydration therapy

Abstract. Intestinal glucose and water absorption in response to glucose has been studied in tropical enteropathy with a view to determine the optimum glucose concentration in oral rehydration solutions for use in the tropics. Maximum jejunal water and sodium absorption occurred from an 80-mM glucose-sodium chloride solution (−285.7 ± 46.0 ml/30 cm/h and 31.8 ± 3.8 mM/30 cm/h, respectively) during in vivo steady-state jejunal perfusion. At perfusate glucose concentrations > 250 mM, however, jejunal water and sodium secretion occurred. In the ileum, maximum glucose-stimulated water absorption (−91.1 ± 27.1 ml/30 cm/h) was significantly less than in the jejunum. Glucose absorption demonstrated saturation kinetics in both the jejunum and ileum. The half-saturation concentration was higher in the jejunum (167 mM) compared to the ileum (28 mM). This study suggests that the optimal glucose concentration for oral rehydration solutions used in the tropics should be 80 mM, as lower and higher concentrations result in diminished jejunal water absorption.

Oral glucose-electrolyte solutions are an integral part of the therapy of acute diarrhoea. However, despite extensive use, controversy continues as to their optimal composition. The value of bicarbonate and citrate in oral rehydration solutions has been questioned [1, 2], and a sodium concentration of 90 mM is considered excessive by some [3, 4]. Similarly, opinion varies as to the optimum glucose concentration in these solutions [5, 6]. The glucose concentrations in some formulations, including that recommended by the World Health Organization [7], have been shown to maximally stimulate jejunal water absorption in healthy subjects from developed countries [8]. Extrapolation of these data to individuals in the tropics is inappropriate, since in developing countries many healthy residents, especially those living in rural areas, absorb nutrients and water in response to luminal stimuli less efficiently than healthy Western people [9, 10]. This impaired intestinal absorptive capacity and the associated morphological changes observed in almost all indigenous residents of developing countries relative to that in individuals from more advanced countries...
are collectively termed tropical enteropathy [9, 11]. We therefore studied glucose as well as water and sodium absorption in response to glucose in vivo, in the human jejunum and ileum of Indian subjects with tropical enteropathy, with a view to determine the glucose concentration which produced maximum water and sodium absorption.

Subjects and Methods

Twenty-four healthy rural Indian subjects (13 male, 11 female, median age 30 years), who came to hospital for a general check-up were studied using a steady-state perfusion technique [12]. All these subjects had tropical enteropathy, because they had non-specific morphological changes in the jejunum and mildly elevated faecal fat or impaired urinary xylose excretion [9]. Following an overnight fast, each subject swallowed a four-lumen perfusion tube which incorporated a proximal occluding balloon. Infusion and collection orifices were placed 30 cm apart and a distal mercury bag. For the jejunal studies, the tube was positioned, under fluoroscopy, such that the infusion orifice was situated in the first 5 cm of the jejunum, and for the ileal studies the mercury bag was about 200 cm from the incisor with no slack in the stomach. The solutions, at 37°C, were perfused in random order at a constant rate of 10 ml/min, using a Water-Marlow constant infusion pump. A minimum of two and a maximum of six solutions were perfused in any one subject. The decision regarding the number of solutions perfused was determined by the duration the subject was able to tolerate the perfusion tubes. The equilibration period between successive studies was at least 50 min and the test period consisted of three successive 10-min collections.

This study was approved by the Research and Ethics Committee of the Christian Medical College Hospital, Vellore.

The solutions contained glucose in concentrations ranging from 10 to 290 mM. The osmolality of all the solutions was adjusted to 290 mosm/kg, where necessary, using either sodium chloride (maximum sodium concentration = 130 mM) or D-mannitol. Polyethylene glycol (PEG, molecular weight 4,000) 2.5 g/l was used as a non-absorbable marker (table 1).

Table 1. Composition of solutions perfused.

<table>
<thead>
<tr>
<th>Glucose concentration mM</th>
<th>Sodium chloride concentration mM</th>
<th>Mannitol mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>130</td>
<td>38</td>
</tr>
<tr>
<td>30</td>
<td>130</td>
<td>15</td>
</tr>
<tr>
<td>60</td>
<td>123</td>
<td>115</td>
</tr>
<tr>
<td>80</td>
<td>103</td>
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<td>200</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>250</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>290</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All solutions contained PEG (molecular weight 4,000) 2.5 g/l and were isotonic with plasma.

Aliquots from each 10-min collection period were stored at -20°C till analysed.

D-glucose was obtained from Sigma, U.K. D-mannitol from BDH Laboratories, U.K., sodium chloride from Sarabhai Chemicals, India, and PEG from Merck, Switzerland. All reagents used were of analytical grade.

Analysis of Samples and Calculations

Glucose was estimated by the potassium cyanide method in a continuous flow automatic system. Sodium concentrations were measured by flame photometry. PEG by the turbidimetric method of Hyden [13] and osmolality in a Wescor vapor pressure osmometer (Wescor, St. Logan, USA). Net osmotic and solute fluxes across the intestinal mucosa were calculated using standard formulae [14]. Net absorption (+) indicates net transfer of water or solute into the lumen; net secretion (-) indicates net transfer of water or solute into the lumen.

Statistical Methods

The unpaired Student's t test was used to determine the significance between the effects of different glucose concentrations on water and electrolyte fluxes. Regression analysis was used to explore the interrelationship between glucose and water or electrolyte fluxes. Differences were considered significant if p < 0.05. All data are expressed as means ± SEM.
Glucose Absorption in Tropical Enteropathy

Fig. 1. Jejunal (●) and ileal (○) glucose absorption curves, from 30-cm segments of intestine, demonstrating saturation kinetics. Lineweaver-Burk analysis for jejunal glucose absorption (inset) gave a $K_m$ of 167 mM and a $V_{max}$ of 83 mM/30 cm/h. The $K_m$ and $V_{max}$ for ileal glucose absorption are 28 mM and 83 mM/30 cm/h, respectively. *: At least 5; data are expressed as means ± SEM.

Results

Jejunal Studies
Glucose Absorption. Jejunal glucose absorption suggests a saturable process (fig. 1). Michaelis-Menten kinetics apply, and hence a Lineweaver-Burk plot [15] was constructed to calculate apparent maximum velocity ($V_{max}$) and half-saturation concentration ($K_m$). In this experimental system, and at a flow rate of 10 ml/min, the $V_{max}$ is 83 mM/30 cm/h and the $K_m$ 167 mM (fig. 1).

Effect of Glucose on Water Absorption. There is a progressive increase in water absorption in response to increasing glucose concentrations to a maximum mean of -285 ml/30 cm/h at a glucose concentration of 80 mM (table 2). At lower and higher glucose concentrations there is a progressive decrease in net water absorption. At glucose concentrations > 250 mM net water secretion occurred.

Regression analysis to explore the interrelationship between water transport and glucose absorption showed a significant correlation at glucose concentrations of 60–200 mM. The best correlation, however, occurred with the 80-mM glucose solution ($r = 0.963$, $p < 0.001$).

Effect of Glucose on Sodium Absorption. Sodium movement paralleled water movement. Sodium absorption progressively increased to a maximum mean of -31.8 mM/30 cm/h in the presence of 80 mM glucose (table 2). This increase in sodium absorption is glucose dependent, as sodium concentrations in the perfusates over this range (10–80 mM glucose) are comparable (130–115 mM).

Ileal Studies
As in the jejunum, saturation kinetics for glucose absorption were demonstrated (fig. 1). Using the Lineweaver-Burk plot, the derived apparent maximum velocity was 23 mM/30 cm/h and the $K_m$ 28 mM. The mean maximum glucose absorption rate in the ileum was less than in the jejunum by a fac-
Table 2. Effect of glucose on jejunal and ileal net water and sodium transport

<table>
<thead>
<tr>
<th>Initial glucose concentration (mM)</th>
<th>Jejunum</th>
<th></th>
<th></th>
<th>Ileum</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>water</td>
<td>sodium</td>
<td>n</td>
<td>water</td>
<td>sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ml/30 cm/h</td>
<td>mM/30 cm/h</td>
<td></td>
<td>ml/30 cm/h</td>
<td>mM/30 cm/h</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>-24.9 ± 10.1*</td>
<td>-3.3 ± 2.2*</td>
<td>6</td>
<td>-37.8 ± 6.5</td>
<td>-8.5 ± 1.7</td>
</tr>
<tr>
<td>50</td>
<td>7</td>
<td>-77.9 ± 16.5*</td>
<td>-13.8 ± 2.5*</td>
<td>6</td>
<td>-46.2 ± 26.6</td>
<td>-5.1 ± 1.2</td>
</tr>
<tr>
<td>80</td>
<td>7</td>
<td>-215.4 ± 13.2</td>
<td>-20.9 ± 2.6*</td>
<td>6</td>
<td>-91.1 ± 27.1</td>
<td>-7.4 ± 2.0</td>
</tr>
<tr>
<td>100</td>
<td>9</td>
<td>-285.7 ± 46.0</td>
<td>-31.8 ± 3.8*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>150</td>
<td>8</td>
<td>-199.9 ± 40.8</td>
<td>-19.6 ± 4.3</td>
<td>6</td>
<td>-71.4 ± 15.9</td>
<td>-5.6 ± 1.5</td>
</tr>
<tr>
<td>200</td>
<td>5</td>
<td>-166.6 ± 42.9</td>
<td>-8.3 ± 3.5*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>250</td>
<td>6</td>
<td>-166.6 ± 52.6</td>
<td>-3.7 ± 3.1*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>290</td>
<td>6</td>
<td>+6.0 ± 12.2*</td>
<td>+20.0 ± 1.5*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SEM. n = Number of subjects studied; – = absorption; + = secretion; ND = not done. * p < 0.05 compared to water and sodium absorption from the 80-mM glucose-containing solution.

Discussion

The present study confirms previously published data in humans that (1) glucose stimulates jejunal and ileal water absorption and jejunal sodium absorption (table 2) [16, 17], (2) glucose absorption is carrier mediated [18] and that (3) the jejunum absorbs glucose to a greater extent than the ileum [19].

Maximum jejunal net water absorption occurred from the 80-mM glucose solution. This glucose concentration is probably the optimal concentration for use in oral rehydration solutions in the tropics, because one of the aims of oral rehydration therapy is to prevent or rapidly correct water deficits. Water intoxication due to avid water absorption is unlikely in the presence of normal renal function [21]. However, there was a significant difference in net water absorption over a wide range of glucose concentrations (60–200 mM) suggesting that there is individual interindividual variation in intestinal absorption in response to glucose, because although mean net jejunal water absorption range from 166 to 285 ml/30 cm/h, the standard error in each group of subjects studied was large (table 2). This marked interindividual variation in glucose-stimulated jejunal absorption has previously been noticed in healthy individuals from the West [8] and perfusate concentrations > 100 mM net water absorption progressively decreased in the jejunum and in the ileum, and concentrations > 250 mM net water absorption occurred. This decrease in net water absorption is attributed to the osmotic effect of unabsorbed luminal glucose [22] and
low sodium and chloride content in the perfusates which produce secretion of large amounts of sodium and chloride into the intestinal lumen [8]. The result is suboptimal net absorption of water from the intestine. This could be an explanation for the increase in purging rates observed in some patients with acute diarrhoea when given oral rehydration solutions containing glucose in concentrations  

\[ > 100 \text{ mM} \]  

[23-25]. This latter observation provides further evidence for the need for evaluating oral rehydration solutions with glucose concentrations < 100 mM in acute diarrhoea therapy in the tropics.

Maximum sodium absorption occurred with the 80-mM glucose-sodium chloride solution. However, optimum sodium concentrations for use in oral rehydration solutions cannot be derived from perfusion studies, because in this system net sodium secretion occurs at perfusate concentrations < 110 mM [6, 26]. In fact, sodium absorption from a glucose-electrolyte solution is directly related to the sodium concentrations and inversely related to the glucose concentrations in the perfusates so that progressively greater amounts of sodium are absorbed, the closer the perfusate sodium concentration is to that of plasma [27].

Direct comparison between the present study and published studies from the West [8, 16, 17] is fraught with difficulties because of differences in flow rates, length of test segments and perfusate compositions. Nevertheless, when glucose absorption and glucose-stimulated water and sodium absorption in response to similar glucose loads (mM/min) was derived from data in published studies [8, 16], and compared to data from the present study these were consistently lower in healthy Indians compared to healthy Westerners. This observation lends support to earlier reports from this department that intestinal nutrient, and water and sodium absorption in healthy Indians occurs less efficiently than in healthy people from the West [10, 28].

The markedly different \( K_m \) values in the jejunum and the ileum (obtained under identical conditions in the present study) suggest the presence of predominantly low-affinity glucose carriers in the jejunum, which has a larger surface area than the ileum, and predominantly high-affinity carriers in the ileum.

Our data provide a rationale for suggesting that, for oral rehydration solutions for use in the tropics, the glucose concentration should be ~ 80 mM, as this concentration produces maximum water and sodium absorption. However, caution must be exercised in extrapolating data from short-segment perfusion experiments to the entire intestine and indeed from the normal gut to the secreting gut as in diarrhoeal disease.

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