Oral IGF-I enhances nutrient and electrolyte absorption in neonatal piglet intestine

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Alexander, Andrew N., and Hannah V. Carey. Oral IGF-I enhances nutrient and electrolyte absorption in neonatal piglet intestine. Am. J. Physiol. 277 (Gastrointest. Liver Physiol. 40): G619–G625, 1999.—The effect of orally administered insulin-like growth factor-I (IGF-I) on small intestinal structure and function was studied in 5-day-old colostrum-deprived piglets. Human recombinant IGF-I (3.5 mg·kg⁻¹·day⁻¹) or control vehicle was given orogastrically for 4 days. Body weights, jejunal and ileal mucosa wet and dry weights, and serum IGF-I levels were similar in the two groups. Small intestinal villus height and crypt depth and jejunal enterocyte microvillar dimensions were also similar between groups. Oral IGF-I produced higher rates of jejunal ion transport because of increased basal Na⁺ absorption. Short-circuit current responses to mucosal addition of D-glucose and L-alanine and net transepithelial absorption of 3-O-methylglucose were increased by IGF-I. Carrier-mediated uptake of D-glucose per milligram in everted jejunal sleeves was greater in IGF-I-treated piglets because of a significantly greater maximal rate of uptake. We conclude that rates of net Na⁺ and Na⁺-dependent nutrient absorption are enhanced in piglets treated with oral IGF-I, and this effect is independent of changes in mucosal mass or surface area.

Maturation of the small intestine shortly after birth is thought to be due, at least in part, to one or more growth factors present in breast milk and colostrum (13, 41, 42). Interest has been focused primarily on two of these: epidermal growth factor (EGF) and insulin-like growth factor-I (IGF-I). Both peptides have been shown to stimulate gastrointestinal mucosal growth and brush-border enzyme activity when given exogenously to suckling animals (1, 4, 18, 28, 44, 47). Far fewer studies have examined the effects of these molecules on epithelial transport function in neonates. Luminal or systemic administration of EGF was shown to stimulate nutrient and electrolyte transport in adult animals (2, 17), and there is both supportive (28) and inconclusive (15) evidence for its role in nutrient absorption in suckling animals. In contrast, the ability of IGF-I to influence intestinal absorptive function in neonates is poorly understood.

IGF-I is a 70-amino-acid-long polypeptide whose structure is highly conserved among species and shares 100% homology among human, porcine, and bovine IGF-I (38). The liver is the major site for synthesis of IGF-I in serum, but IGF-I is also synthesized locally in other tissues, including the gastrointestinal tract (20, 46). IGF-I is the mediator of most of the anabolic effects of growth hormone, particularly through its effects on protein and carbohydrate metabolism (36). IGF-I has a wide range of biological actions, including stimulation of proliferation and differentiation in many tissues (20). Physiologically, IGF-I has been shown to have both acute and chronic effects on tissues, depending on route and duration of administration. In vitro, IGF-I can stimulate a number of cellular transport processes, including facilitated glucose uptake (32), Na⁺/H⁺ exchange (19), Na⁺/K⁺-ATPase activity (37), and Na⁺-dependent phosphate absorption (11, 35). In vivo experiments have further characterized the effects of IGF-I at the whole animal level. Chronic infusion of recombinant human IGF-I into human volunteers stimulated Na⁺ reabsorption from the kidney via the Na⁺/H⁺ exchanger on the brush border of proximal tubule cells (16).

It is well established that IGF-I can influence gastrointestinal growth in adults when the peptide is given systemically. Intravenous or subcutaneous administration of IGF-I in adults increases intestinal mucosal weight, protein and DNA content, villus height, and epithelial proliferation (22, 29, 30, 34, 49). There are also reports that systemic IGF-I can influence intestinal epithelial function. Peterson et al. (30) showed that adult rats maintained on total parenteral nutrition (TPN) solutions coinfused with recombinant human IGF-I (rHIgf-I) had significantly less jejunal atrophy as well as partial to complete reversal of the enhanced tissue permeability and hypersecretion of Cl⁻ that is induced by TPN alone. Subcutaneous IGF-I treatment has been shown to ameliorate the diminished intestinal absorptive function observed in a rat model of liver cirrhosis (10).

In contrast to these effects of IGF-I when given systemically, it appears to have little effect on the adult gastrointestinal tract after enteral administration. In neonates, however, oral administration of the peptide stimulates intestinal mucosal growth and brush-border enzyme activity (18), perhaps because of its protection from proteolytic degradation by casein in breast milk (43). Burrin et al. (4) demonstrated greater intestinal weight, protein and DNA content, and villus heights of the jejunum and ileum in neonatal piglets administered rhIGF-I via orogastric gavage. Oral IGF-I also stimulated enterocyte proliferation and disaccharidase activity in neonatal pig ileum (18). Although these studies provide compelling evidence that oral IGF-I can enhance intestinal growth and enzyme activity in neonates, its effect on epithelial transport is less well
understood. Thus the aim of our study was to determine whether orally administered IGF-I influences intestinal nutrient and electrolyte transport in neonatal piglets. We focused our functional studies on the jejunum, which is the major site of nutrient absorption in the small intestine. To complement the functional studies, we determined the effect of oral IGF-I on jejunal mucosal morphology at light and electron microscope levels. We also carried out limited measurements on ileal structure because others have reported that orally administered IGF-I may selectively enhance ileal mucosal growth (4, 18).

MATERIALS AND METHODS

Experimental animals and diets. The University of Wisconsin Institutional Animal Care and Use Committee approved the protocol used in this study. Colostrum-deprived neonatal crossbred pigs (1–2 kg body wt) were obtained through the University of Wisconsin Swine Teaching and Research herd. In Institutional Animal Care and Use Committee approved studies, we determined the effect of oral IGF-I on jejunal mucosal morphology at light and electron microscope levels. We also carried out limited measurements on ileal structure because others have reported that orally administered IGF-I may selectively enhance ileal mucosal growth (4, 18).

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Kinetics of active \(\alpha\)-glucose transport in intact jejunal tissues. Methods were similar to those previously described (9, 33, 39, 48). After harvest from the animal, jejunal tissues were bathed continually in ice-cold Krebs solution and bubbled with 95% \(O_2\)/5% \(CO_2\) during tissue preparation. Tissues were everted, and 1-cm sleeves were mounted on grooved metal rods (7 mm diameter) suspended in a warmed (39°C) oxygenated Krebs solution over a stir bar rotating at 1,200 rotations/min. Sleeves were preincubated in isotope-free solution for 5 min and then transferred to incubation solutions containing varying concentrations of unlabeled \(\alpha\)-glucose and radiolabeled probes. Incubation solutions containing unlabeled \(\alpha\)-glucose were prepared by isosmotic replacement of mannitol to obtain a solution osmolality of \(\approx 290\) mosmol/kgH\(_2\)O. Uptake studies used 4 \(\mu\)Ci of \(\alpha\)-[\(3\)H]glucose (American Radiolabeled Chemical, St. Louis, MO) added to each incubation solution of cold \(\alpha\)-glucose. After incubation, sleeves were rinsed in Krebs solution for 20 s, blotted on filter paper, placed into tared vials, and weighed. Tissue solubilizer (500 \(\mu\)l, Solvable, Packard) was added, and 24 h later 4 ml of aqueous counting scintillant (Ultima Gold, Packard) were added to each vial. Radiotracer counting procedures and data analyses were performed as previously described (21). Uptake rates were corrected for solute present in adherent fluid by addition of tracer amounts of \(\alpha\)-[\(14\)C]polyethylene glycol. Passive permeability coefficients \((P^t)\) were calculated from uptake rates of tracer quantities of \(\alpha\)-glucose, which is not transported by the \(Na^+\)-glucose transporter (SGLT1), with the use of methods described by Karasov and Diamond (21). Carrier-mediated \(\alpha\)-glucose uptake was computed by subtracting passive uptake \((P^tS)\) from the total glucose uptake rate at each \(\alpha\)-glucose concentration. Kinetic data were analyzed with regression models outlined by Carey and Sills (9). The method of Motulsky and Ransnas (26) was used to fit data to linear or nonlinear regression models. Significance of differences between control and IGF-I-treated pigs were determined by methods previously described (24).

Statistics. Values are reported as means \(\pm\) SE. Student's t-tests were used to determine significance of differences between means. A probability level of \(P < 0.05\) was considered statistically significant.

### RESULTS

There were no differences in overall animal demeanor or fecal consistency between IGF-I-treated and control piglets. However, a small percentage (~10%) of the piglets that included animals from both treatment groups failed to thrive and were removed from the study.

Piglet body weights and serum IGF-I levels. Control and IGF-I-treated piglets had similar rates of weight gain (177.0 \(\pm\) 35.2 g/day and 172.5 \(\pm\) 38.2 g/day, respectively). Mean body weights on day 5 in IGF-I-treated and control piglets were similar (2.1 \(\pm\) 0.1 kg vs. 1.9 \(\pm\) 0.1 kg, respectively; \(P = 0.20\)). Serum IGF-I levels determined by radioimmunoassay were similar in IGF-I-treated and control piglets (66.3 \(\pm\) 11.0 \(\mu\)g/l, \(n = 6\), vs. 58.5 \(\pm\) 6.3 \(\mu\)g/l, \(n = 10\), respectively; \(P = 0.55\)).

Intestinal mucosa and brush-border morphology. Oral administration of IGF-I had no significant effect on mucosal wet or dry weight per centimeter, villus height, or crypt depth in the jejunum and ileum compared with control piglets (Table 1). Ultrastructural analysis was carried out on three jejunal enterocytes from each of five piglets per treatment group. There were no signifi-

### Table 1. Intestinal mucosa morphology in piglets

<table>
<thead>
<tr>
<th>Segment</th>
<th>Diet</th>
<th>No. of Pigs</th>
<th>No. of Tissues</th>
<th>Mucosal Wet Wt, mg/cm</th>
<th>Mucosal Dry Wt, mg/cm</th>
<th>Villus Height, (\mu)m</th>
<th>Crypt Depth, (\mu)m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jejunum</td>
<td>Control</td>
<td>15</td>
<td>128 (\pm) 10</td>
<td>21 (\pm) 5</td>
<td>563 (\pm) 58</td>
<td>139 (\pm) 5</td>
<td></td>
</tr>
<tr>
<td>IGF-I</td>
<td>18</td>
<td>133 (\pm) 11</td>
<td>17 (\pm) 1</td>
<td>492 (\pm) 49</td>
<td>142 (\pm) 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td>Control</td>
<td>15</td>
<td>143 (\pm) 10</td>
<td>26 (\pm) 5</td>
<td>391 (\pm) 28</td>
<td>123 (\pm) 4</td>
<td></td>
</tr>
<tr>
<td>IGF-I</td>
<td>18</td>
<td>148 (\pm) 14</td>
<td>28 (\pm) 7</td>
<td>423 (\pm) 43</td>
<td>136 (\pm) 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means \(\pm\) SE. IGF-I, insulin-like growth factor-I.

Table 2. Basal electrical parameters in piglet jejunum

<table>
<thead>
<tr>
<th>Diet</th>
<th>No. of Pigs</th>
<th>No. of Tissues</th>
<th>PD, mV</th>
<th>(I_{sc}), (\mu)A/cm(^2)</th>
<th>(G_t), mS/cm(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>14</td>
<td>112</td>
<td>4.2 (\pm) 0.8</td>
<td>114.5 (\pm) 6.7</td>
<td>31.4 (\pm) 1.0</td>
</tr>
<tr>
<td>Oral IGF-I</td>
<td>16</td>
<td>124</td>
<td>4.9 (\pm) 0.2*</td>
<td>141.6 (\pm) 5.6*</td>
<td>30.7 (\pm) 0.8</td>
</tr>
</tbody>
</table>

Values are means \(\pm\) SE. \(I_{sc}\), short-circuit current; PD, transepithelial potential difference; \(G_t\), tissue conductance. *\(P < 0.01\) vs. control piglets.
Consistent with previous experiments, basal $I_{sc}$ was significantly higher in IGF-I piglets compared with controls (76.3 ± 4.6 μA/cm² vs. 45.0 ± 5.5 μA/cm², respectively; $P < 0.01$).

Wet weights of everted jejunal sleeves were not significantly different between four IGF-I-treated and four control piglets (154.6 ± 2.6 mg/cm vs. 161.7 ± 3.6 mg/cm, respectively; $P = 0.20$). The curves representing nonlinear least-squares fits of total D-glucose uptake data to the Michaelis-Menton ($K_m$) equation for the two treatment groups were significantly different [$F = 9.98$, degrees of freedom (df) = 2,114; $P < 0.001$]. $P^*$ calculated from L-glucose uptakes were similar (Table 4). Carrier-mediated uptake rates of D-glucose normalized to tissue mass for control and IGF-I-treated piglets are shown in Fig. 2. The data for both groups were best fit to a nonlinear model, and the curves were significantly different from one another ($F = 10.32$, df = 2,130; $P < 0.001$). Kinetic analysis revealed a significantly greater maximal rate of D-glucose transport ($J_{max}$) per milligram in IGF-I-treated piglets compared with controls (Table 4). There were no differences in apparent $K_m$ between groups.

**DISCUSSION**

The goal of this study was to investigate the effect of orally administered IGF-I on intestinal ion and nutrient transport in neonatal piglets. The concentration of IGF-I we used (3.5 mg·kg⁻¹·day⁻¹) was shown by others (4) to stimulate intestinal mucosal growth in newborn piglets. We used the same dosing regime to determine whether this pharmacological concentration also influenced intestinal function in a similar animal model. We administered IGF-I orally to mimic the natural presence of the peptide in the neonatal gut lumen. There is evidence for apically located IGF-I receptors on jejunal enterocytes during the suckling period (25) that could potentially mediate effects of luminal IGF-I on epithelial function. Furthermore, IGF-I is thought to retain bioactivity in the neonatal intestinal lumen, possibly because of the lower pH of gastric contents in neonates and protection of the peptide from luminal proteolysis by high concentrations of casein in milk and milk replacers (13, 43).

In our study, oral administration of IGF-I had no effect on serum IGF-I levels, which is consistent with the findings of Burrin et al. (4). However, other studies suggest that luminal IGF-I may cross the intestinal mucosa in neonates and accumulate within the gastrointestinal wall and/or in the systemic circulation (31, 45). The contrasting findings in these studies may reflect differences in the detection methods used to measure IGF-I in serum. Our study and that of Burrin et al. (4) used radioimmunoassay, whereas those studies that documented an elevation in serum IGF-I administered radiolabeled IGF-I and subsequently detected the radiolabel in serum and tissues (31). The half-life of IGF-I in serum ranges from minutes for free IGF-I to hours for IGF-I bound to IGF-I-binding proteins (40). Serum levels of IGF-I-binding proteins were not measured in our study, and thus their influence on serum IGF-I levels is unknown.

Oral IGF-I had no effect on piglet body weight nor did it affect the mass or mucosal architecture of either the jejunum or ileum. The study of Burrin et al. (4), which used the same oral IGF-I concentration, reported no effect of the peptide on piglet body weight; however, oral IGF-I significantly increased intestinal weight as well as jejunal and ileal villus height. Recently, the same investigators reported minimal effects of IGF-I on intestinal growth of mouse pups suckling from dams that overexpressed IGF-I in mammary secretions (3). Houle et al. (18) administered oral IGF-I to 14-day-old piglets at a concentration similar to that found in sow colostrum (200 µg·kg⁻¹·day⁻¹) for 14 days and reported no effect of the peptide on body weight, but it significantly increased ileal (but not jejunal) villus height. In our study, oral IGF-I also had no effect on

**Fig. 1.** Changes in short-circuit current ($\Delta I_{sc}$) after mucosal addition of 10 mM D-glucose (A) or 10 mM L-alanine (B) in piglet jejunum. D-glucose studies used 23 tissues from 6 control and 36 tissues from 7 insulin-like growth factor-I (IGF-I)-treated piglets; L-alanine studies used 32 tissues from 6 control and 51 tissues from 7 IGF-I-treated piglets. **$P < 0.01$ and ***$P < 0.001$ vs. controls.
Table 4. Kinetic parameters for active uptake of D-glucose in control and IGF-I-treated piglets

<table>
<thead>
<tr>
<th>Diet</th>
<th>No. of Pigs</th>
<th>J_{max}, mmol/min·mg</th>
<th>K_{m}, mM</th>
<th>P^{*}, µl/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4</td>
<td>0.86 ± 0.07</td>
<td>0.75 ± 0.33</td>
<td>0.020 ± 0.007</td>
</tr>
<tr>
<td>IGF-I treated</td>
<td>4</td>
<td>1.40 ± 0.05*</td>
<td>1.04 ± 0.23</td>
<td>0.020 ± 0.003</td>
</tr>
</tbody>
</table>

Values are means ± SE from 13–15 tissues per animal. Maximum uptake rate (J_{max}) and affinity constant (K_{m}) were calculated from nonlinear fits to the Michaelis-Menton equation using total uptakes of D-[3H]glucose that were corrected for diffusional uptake. Diffusional uptake at each concentration was estimated using passive (diffusional) uptake from the total glucose uptake and dashed line) and 4 IGF-I-treated piglets. *P < 0.001 vs. control piglets.

enterocyte microvillus dimensions, including microvillous height and density. In the only other study that examined IGF-I effects on enterocyte microvillus structure, parenteral IGF-I (0.2 µg·kg⁻¹·day⁻¹) normalized the increased microvillus length induced by cirrhotic liver disease in rats (10). Together, our results and those of others suggest that the small intestine of healthy neonates with adequate nutrition may already be achieving maximal growth rates and that IGF-I supplementation is unable to stimulate additional growth.

Although oral IGF-I did not alter intestinal growth or structure, the peptide had significant effects on epithelial transport. Basal I_{sc} and PD of jejunal tissues were greater in piglets treated with oral IGF-I, suggesting that the peptide resulted in a higher level of active ion transport in the basal state (as indicated by the higher I_{sc}) and produced a steeper electrical gradient across the epithelium (as indicated by the elevated PD). Oral IGF-I did not alter ionic permeability of the jejunum because G_5 was similar in both groups. Changes in G_5 in a leaky epithelium like the jejunum are largely due to changes in paracellular permeability, and the absence of an effect of IGF-I on this transport route suggests the peptide did not compromise the barrier function of the intestinal mucosa.

The effects of oral IGF-I on basal electrical parameters were mirrored by its effects on transepithelial ion fluxes. The higher basal I_{sc} of IGF-I-treated piglets was due primarily to increased net absorption of Na⁺, due to an increase in mucosal-to-serosal fluxes of the cation. Although mucosal-to-serosal Cl⁻ flux was increased by the peptide, the effect on net Cl⁻ movement was not significant. Similarly, J_{ sc}, which most likely reflects bicarbonate secretion, was reduced by IGF-I, but the effect was not significant. These trends for reduced secretion of both anions, which tend to reduce I_{sc} values, likely accounted for the disparity between the increase in I_{sc} induced by the peptide (about twofold) and the larger increase in net Na⁺ flux (about threefold).

In addition to its effect on net Na⁺ absorption, oral IGF-I also increased the absorptive capacity for two different Na⁺-coupled nutrients, D-glucose and L-alanine. This was supported by three separate experiments. First, the increase in I_{sc} induced by mucosal addition of either nutrient was greater in IGF-I-treated piglets. Because both nutrients are cotransported with Na⁺, the D-glucose- and L-alanine-stimulated changes in I_{sc} are indirect measures of each nutrient’s absorption rate. These electrical findings were confirmed by the enhanced rates of net transepithelial absorption of 3-OMG observed in IGF-I-treated piglets. An effect of IGF-I on stimulating Na⁺-coupled solute transport has been demonstrated in other cell types, including kidney epithelial cells (11) and osteoblasts (35), in which it stimulates Na⁺-dependent phosphate absorption.

Studies with everted jejunal sleeves provided a third measure of the peptide’s effects on nutrient absorption by focusing on changes in sugar uptake across the brush-border membrane into enterocytes. Piglets receiving oral IGF-I had significantly greater total and carrier-mediated D-glucose uptake rates when normalized to tissue mass. Total uptake represents the rate of solute transport through both the nonselective paracellular pathway and the brush-border Na⁺-glucose transporter (SGLT1). We calculated P^{*} using L-glucose fluxes, and we used these to derive carrier-mediated uptake rates in the two groups of piglets. The observation that P^{*} values were similar in control and IGF-I-treated piglets lends further support to the idea that oral IGF-I does not alter paracellular permeability of the jejunal epithelium.

Kinetic analysis of carrier-mediated D-glucose uptake indicated that jejunal tissues from animals given IGF-I had significantly greater J_{max} but the affinity of the sugar for SGLT1 (K_{m}) was unchanged. Several mechanisms could account for a greater J_{max} in IGF-I-treated piglets. One is an increase in SGLT1 expression secondary to increased proliferation of enterocytes in IGF-I-treated piglets. This mechanism is unlikely to account for our results because we found no differences in jejunal tissue weight, villus height, crypt depth, or
microvillar surface morphology as the result of IGF-I treatment. Second, there could be an increase in density of SGLT1 molecules in brush-border membranes of individual enterocytes after IGF-I treatment. Recently, Cheeseman et al. (12) demonstrated an increase in SGLT1 abundance in brush-border membranes in rats perfused in vivo with glucagon-like peptide 2; thus there is precedent for hormonal regulation of this transporter. Furthermore, EGF, another peptide growth factor present in high concentrations in porcine colos- trum, has been reported to increase SGLT1 abundance in intestinal tissues after massive small bowel resection in adult rats (14).

Another mechanism to explain the ability of IGF-I to increase the $J_{\text{max}}$ for $\text{D-glucose}$ in piglet jejunum is an increase in the electrochemical driving force for $Na^+$-coupled nutrient transport. This possibility is supported by the enhanced rates of net $Na^+$ absorption as well as the greater change in $I_{\text{EC}}$ induced by L-alanine in IGF-I-treated piglets. Both of these processes would also be favored by a change in the $Na^+$ electrochemical gradient across the brush-border membrane. Because the $Na^+$ electrochemical gradient is dependent on basolateral $Na^+\cdot K^+$-ATPase activity, an increase in the number and/or activity of $Na^+\cdot K^+$-ATPase pumps could be involved in the upregulation of nutrient absorption in IGF-I-treated piglets. Treatment of rat arterial smooth muscle cells in vitro with IGF-I was reported to stimulate $Na^+\cdot K^+$-ATPase activity (37), and in preliminary studies we observed greater $Na^+\cdot K^+$-ATPase activity in enterocytes from IGF-I-treated piglets compared with control animals (unpublished observations).

In summary, our results provide evidence that oral administration of IGF-I to neonatal pigs can enhance intestinal epithelial $Na^+$ and $Na^+\cdot$coupled nutrient absorption in the absence of changes in enterocyte mass or architecture. Because orogastic administration of IGF-I did not alter serum IGF-I levels, we speculate that luminal IGF-I exerted its effects via stimulation of brush-border IGF-I receptors (23, 25, 47) and/or transepithelial transport of IGF-I and subsequent activation of IGF-I receptors located on basolateral membranes. Future studies should focus on elucidating the cellular mechanisms of IGF-I action in the neonatal intestine.

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