Intrauterine growth restriction reduces intestinal structure and modifies the response to colostrum in preterm and term piglets

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ABSTRACT

We investigated some consequences of intrauterine growth restriction (IUGR) on weight and structural and functional parameters of the intestine at birth and after 2 days of colostrum feeding. IUGR altered intestinal morphology, leading to a longer and thinner small intestine in piglets born both preterm and at full term, together with reduced villous size in term IUGR piglets. Preterm IUGR piglets displayed an improved ability to adapt to colostrum intake by rapid intestinal catch-up growth, relative to other groups of pigs. In contrast, intestinal nutrient absorption surface was impaired by IUGR during the first days of life in term piglets. The postnatal effects of IUGR may have long term consequences for developing piglets, and these effects may depend on gestational age at birth, preterm or term.

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1. Introduction

In both humans and animals, intrauterine growth restricted (IUGR) neonates have higher perinatal mortality and morbidity. In pigs, genetic selection has led to the production of hyperprolific dams, reducing the mean piglet birth weight and increasing the within-litter birth weight heterogeneity (Quiniou et al., 2002). IUGR piglets are weak and generally die during the first days of life (Milligan et al., 2002). Xu et al. (1994) and Wang et al. (2005) previously described a longer and thinner small intestine (SI) with reduced villous height in term IUGR piglets at birth, and a modified mucosal immune response. In humans, IUGR babies are often born prematurely (Fang, 2005). Whether IUGR differently alters gastrointestinal tract (GIT) growth and maturation in neonates born prematurely or at full term remain unknown. We hypothesized that IUGR piglets would alter intestinal adaptation to enteral feeding, and that this might differ between preterm and term pigs. Hence, we investigated the early postnatal changes in structural and functional parameters of SI in piglets delivered either preterm or full term.

2. Materials and methods

Piglets delivered either at preterm stage of gestation (50 piglets from 8 sows, caesarean section at 92% gestation, experiment 1; Sangild, 2006) or at full term (24 piglets from 11 sows, spontaneous delivery at 116±2 days gestation, experiment 2) were euthanized either within 6 h of birth (day 0, no oral feeding) or after 2 days of colostrum feeding. Piglets were categorized as normal birth weight (NW) when their birth weight was within 1 SD unit of the average birth weight of the whole litter, and as IUGR when their birth weight was at least 1.5 SD units lower than the average birth weight. The term pigs allocated for oral feeding were allowed to suckle their sow until being sacrificed at 2 days of age. The estimated intake of sow’s colostrum was 100–250 mL/kg/day (Devillers et al., 2004). In contrast, preterm piglets allocated for oral feeding were fitted with orogastric catheters and fed enterally with...
sow’s colostrum every 3 h (120 mL/kg/day) because preterm piglets generally lack natural sucking reflexes. While the term piglets were reared by their sow, the preterm piglets were kept in infant incubators as described (Sangild et al., 2006). The experiment was conducted in compliance with the guidelines of the French Ministry of Agriculture for animal research and The National Committee on Animal Experimentation in Denmark.

At slaughtering weights and lengths of emptied SI and colon were measured. Samples collected at 17, 50 and 83% of the entire SI length were used for measurements of intestinal density and mucosa weight. Disaccharidases (lactase EC3.2.1.23 and sucrase EC3.2.1.24) and peptidases (aminopeptidase N EC3.4.11.2 and dipeptidylpeptidase IV (DPP IV) EC3.4.14.5) activities were assayed in duplicate as previously described (Marion et al., 2005; Sangild et al., 2002). The hydrolytic release of one micromolar substrate per minute at 37 °C was considered to represent one unit (U) of enzyme activity expressed per gram of wet SI. Values presented are mean activities estimated by the means of values in each third of SI for all animals (Table 1). Last, proximal jejunal 10 cm-segments collected at 17% of SI were placed in 4% formaldehyde buffer for 24 h, transferred to 70% ethanol, embedded in paraffin and stained with hematoxylin and eosin. Villi and crypt areas were analysed as previously described (Blattler et al., 2001).

Analysis of variance testing the effects of age and birth weight was performed using the procedure of SAS software (SAS Institute, Cary, NC, USA) separately for preterm and term piglets (experiments 1 and 2, respectively). Data are means ±SEM. Differences between groups were declared significantly (SAS Institute, Cary, NC, USA) separately for preterm and term piglets at birth and after 2 days of colostrum feeding.

### 3. Results

The weights of both preterm and term IUGR piglets were at birth 52% and 67% of the values in preterm and term NW piglets, respectively (P<0.05, Table 1). These differences were conserved at day 2. Developmental priority was observed for brain in term IUGR piglets at both day 0 and day 2 (P<0.05). Concerning digestive tissues, the colostrum-induced growth of stomach was higher in IUGR preterm (+93%) than in NW preterm and term (+45%) and IUGR term piglets (+20%). That of SI was the greatest in preterm IUGR (+95%), higher than in preterm NW piglets (+72%) and higher than both term IUGR and NW piglets (+50 to 58%).

For both delivery and age groups the relative length and the linear density of SI were respectively significantly higher (+9 to +49%) and lower (−15 to −45%) in IUGR compared to NW (P<0.05, Table 1). Moreover, villous height was reduced in 2 day-old term IUGR piglets (P<0.05) and DPP IV at days 0 and 2 (P<0.05). Enteral nutrition significantly reduced lactase activity at day 2 (P<0.05) and increased aminopeptidase N activity in preterm piglets.

### 4. Discussion

In this study, we investigated the consequences of IUGR on organ weights and on intestinal parameters in both preterm and term piglets. Brain was preserved from the in utero restriction in nutrients. This suggests asymmetrical organ growth in IUGR neonates with a vascular origin of the general growth restriction (Van Assche, 1998). IUGR had a major impact on SI, which was heavier in preterm IUGR neonates and relatively longer and thinner in both preterm and term piglets at birth, as suggested (Xu et al., 1994), and this effect was maintained after 2 days of colostrum intake. This intestinal vulnerability may explain the more frequent and severe intestinal problems observed in the first days of life of IUGR neonates.

### Table 1

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Status of delivery</th>
<th>Age (days)</th>
<th>Birth weight</th>
<th>Body weight (g)</th>
<th>Brain (g/kg)</th>
<th>Stomach (g/kg)</th>
<th>Colon (g/kg)</th>
<th>SI (g/kg)</th>
<th>SI relative length (cm/kg)</th>
<th>SI density (mg/cm)</th>
<th>SI mucosa (%)</th>
<th>Villous height (μm)</th>
<th>Crypt depth (μm)</th>
<th>Lactase (U/g tissue)</th>
<th>Sucrase (U/g tissue)</th>
<th>Ap N (U/g tissue)</th>
<th>DPP IV (U/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Preterm</td>
<td>0</td>
<td>12</td>
<td>594 ±100*</td>
<td>NA</td>
<td>4.1 ±0.2</td>
<td>8.5 ±0.7</td>
<td>21</td>
<td>430 ±21</td>
<td>50 ±8</td>
<td>56 ±2</td>
<td>20.2 ±4.2</td>
<td>NA</td>
<td>0.11 ±0.01*</td>
<td>2.64 ±0.23</td>
<td>0.82 ±0.31*</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Term</td>
<td>0</td>
<td>6</td>
<td>1143 ±100b</td>
<td>NA</td>
<td>4.4 ±0.2</td>
<td>7.1 ±0.2</td>
<td>18 b</td>
<td>282 ±11</td>
<td>90 ±7</td>
<td>58 ±2</td>
<td>22.0 ±3.7</td>
<td>NA</td>
<td>0.15 ±0.01</td>
<td>2.28 ±0.21</td>
<td>0.12 ±0.31</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ±SEM. Within the status of delivery means not sharing the same superscript symbol differ significantly (P<0.05). SI, small intestine; Ap N, aminopeptidase N; DPP IV, dipeptidyl peptidase IV; NA, not available.
Prematurity appeared to interfere with the magnitude of the intestinal response to enteral food intake. Indeed, the colostrum-induced increase in SI weight was markedly greater in preterm IUGR piglets than in preterm NW and term piglets. Preterm IUGR piglets displayed ability to adapt to food intake by rapid intestinal catch-up growth and intestinal enzyme changes. Whether this accelerated growth helps IUGR preterms to survive needs further investigation. On the contrary, intestinal absorption surface was impaired by IUGR during the first days of life in term piglets, as illustrated by reduced intestinal villous height. Immaturity in colostrum-induced intestinal adaptation may lead to impaired intestinal barrier and inadequate immune system development in IUGR term piglets, as indicated earlier (Wang et al., 2008).

In conclusion, preterm IUGR piglets seem to adapt their intestine more rapidly to colostrum intake than term IUGR piglets, despite that these piglets had to be fed by stomach tube and thus with much lower amounts of colostrum than the sow-suckled term piglets. The consequences on further growth and health in both preterm and term piglets remain to be investigated precisely.

Conflict of interest

Authors declare that there are no conflicts of interest.

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References


