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The glucagon like peptide-2 'axis': Capacity for production and response following intestinal resection or repair of gastroschisis in infants

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ABSTRACT

Purpose: This study investigates the relationship between the enteric hormone glucagon-like peptide 2 (GLP-2) production, sensitivity, and intestinal adaptation in infants following resection or repair of gastroschisis.
Methods: With IRB approval (UCalgary #10656), consent was obtained from families of infants undergoing surgery for prospective monitoring of nutritional status, GLP-2 levels, and where possible, tissue sampling.
Results: Infants who adapted and weaned from parenteral nutrition (PN) had increased GLP-2 (86 ± 32) n = 24 vs. controls: 45 ± 20 n = 10 and vs. patients on prolonged PN: 42 ± 6 pM, n = 10). This was maintained to one year: weaned patients: 72 ± 49 vs. non-weaned: 35 ± 15 pM ($p < 0.05$). Infants with gastroschisis (n = 33) had decreased GLP-2 levels until enteral function was achieved and then became elevated: (21 ± 15 with first feeding vs. 102 ± 60 at full feeds and 60 ± 19 pM at one year). There were no changes in the density or distribution of GLP-2 producing L-cells related to gestational age, nor in the expression of the GLP-2 receptor.
Conclusion: GLP-2 levels correlate with intestinal adaptation in infants, and with recovery of intestinal function in gastroschisis. GLP-2 productive capacity (L-cell expression) and GLP-2 receptor expression do not vary with maturity. The findings support a role for GLP-2 in regulating intestinal function. Further study is suggested.

The care of infants following major intestinal resection or repair of gastroschisis is an ongoing clinical challenge. Recent advances in the treatment of these patients include the development of multidisciplinary care teams, refinements in the provision of the lipid component of parenteral nutrition (PN), early and aggressive use of breast milk based feeding protocols, enteral antibiotic and ethanol lock therapies to reduce inflammation, and the judicious use of surgical approaches to augment absorptive capacity (such as the STEP procedure). In aggregate, survival has improved significantly [1–3]. With this improvement in survival, there are an increasing number of children who require prolonged PN support Aside from stimulation of enteral feeding, there are no therapies which have been shown to be effective in stimulating the up-regulation in nutrient transport capacity of the residual intestine. This phenomenon, known as intestinal adaptation, is well described, but the factors which regulate it are still poorly understood [4,5].

The endocrine system of the GI tract is a uniquely specialized system of sensor and secretory cells, with multiple effector mechanisms, with the overall function of optimizing the efficiency of nutrient absorption. Glucagon-like peptide-2 (GLP-2 1–33) is a product of this system; it appears to play a key role in the regulation of the function of the intestinal mucosa [6,7]. It is synthesized by L cells, which are most numerous in the terminal ileum, and release GLP-2 in response to undigested nutrients, [8]. In turn, GLP-2 activates a specific receptor, which is exclusively expressed on enteroendocrine cells, enteric neurons and the so-called peri-cryptal myofibroblasts of the intestine. Acutely GLP-2 slows motility, increases mesenteric blood flow and reduces enteric secretions; chronically it is trophic for the small intestinal mucosa [8,9]. In normal physiological situations GLP-2 likely acts as a signal to stimulate the intestinal mucosa to "adapt' or up-regulate nutrient absorptive capacity in situations of nutrient excess, as would happen with a sudden increase in food supply, or during pregnancy. In the pathophysiological state following an intestinal resection similar process occurs [10,11]. GLP-2 levels are strongly correlated with the amount of partially digested nutrients in the intestinal lumen; chronic elevations in GLP-2 levels stimulate an increase in intestinal surface area. This then increase absorption, and reduces the nutrient stimulation of the terminal ileal L-cell sensors and accordingly GLP-2 levels fall [12]. Thus GLP-2 is the regulator in a feedback system or 'axis' controlling intestinal nutrient absorption, similar to the insulin-glucose axis.

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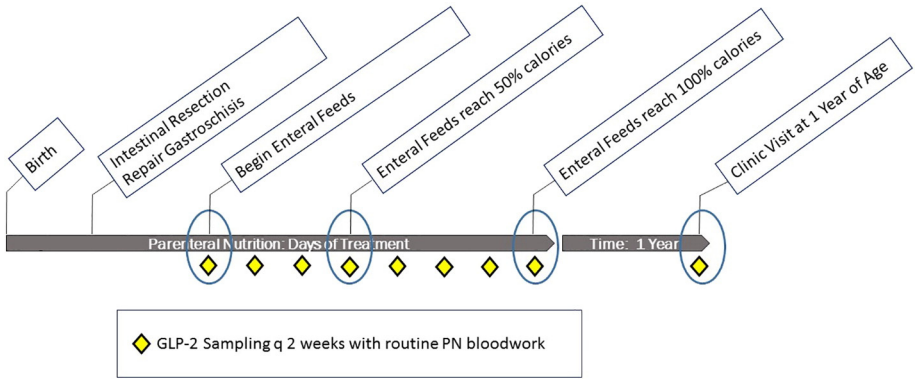

Fig. 1. Timeline of GLP-2 levels.

In the developing infant, very little is known about this system [13–15]. There have been no studies examining the expression of the L-cell or the GLP-2 receptor over the different phases of development and intestinal maturation, nor an examination of the effects of surgery or other pathologies such as gastroschisis. Accordingly, we examined the expression of GLP-2 producing L cells and the expression of the GLP-2 receptor according to gestational age, and intestinal pathology. We further examined the relationship between GLP-2 levels and the ability to wean from PN following major intestinal resection or repair of gastroschisis in the newborn period. We hypothesized that there would be a relationship between the ability to express GLP-2 and intestinal adaptation and that there would be an age-related increase in L cell and GLP-2 receptor expression in all infants, and that this would be reduced in infants with gastroschisis.

1. Methods

This study prospectively examined infants following major intestinal resection or repair of gastroschisis from the period of Sept 2006 to June 2012. With IRB approval, the families of all infants undergoing major intestinal resection (residual intestine less than 50% expected for gestational age, or requiring more than 45 days of PN support), or gastroschisis requiring PN nutrition were prospectively approached and signed informed consent (Fig. 1). Control infants were recruited from children admitted with non-intestinal illness over the same time period. Following the initial surgical repair, patients were transferred to the infant ward, and were cared for by the Children's Hospital Intestinal Rehabilitation Program (CHIRP) of the Alberta Children's Hospital [1,2]. Initial demographic factors and a detailed description of the residual intestinal anatomy were recorded. Residual small intestinal length was expressed as a percentage of expected, based on the patient's gestational age and weight with norms taken from Struigs et al. [16]. Monitoring was done prospectively, with twice weekly data entry and weekly review by the multi-disciplinary CHIRP Team. Monitoring consisted of twice weekly recording of enteral tolerance of feeds, weight gain, parenteral nutrition (PN) requirements, with monitoring of routine PN blood work (CBC, electrolytes, liver function studies) done weekly, following a standardized protocol [2]. Once intestinal function was restored, the aim of care was to continually advance enteral nutrition; all infants were started on expressed breast milk or an elemental formula (Neocate Mead Johnson, or equivalent). Feeds were advanced by 10 ml/kg q 1–2 days, unless limited by a lack of weight gain, high stomal output/diarrhea, distension or vomiting [17]; PN was weaned as EN tolerance increased. Once infants were gaining weight on entirely enteral feeds for 48 h, PN was discontinued.

2. GLP-2 response following resection

The relationship between GLP-2 production and the ability to wean PN, following intestinal resection was investigated by examining the GLP-2 profile during the TPN weaning phase. In previous animal and human studies, there was evidence of a change in the GLP-2 production with development [14,15,18]; accordingly patients and controls were categorized by corrected gestational age into premature (<38 weeks), infant (38 week to 8 months, pre-weaning) and post-weaning (>8 months) groups. Post-resection patients were further grouped into those able to be weaned from PN support within 12 months of their initial operation and those requiring PN for 12 months or greater. Gastroschisis patients with atresia requiring resection were considered as gastroschisis patients. GLP-2 levels were collected bi-weekly as part of the routine of PN bloodwork: from these fasting and meal-stimulated levels were examined at the introduction of enteral feeding, at the attainment of 50% of enteral calories,

Table 1
Demographics of patients followed with GLP-2 sampling during PN weaning.

	Controls\(normal infants) (n = 10)	Resection, Adapted (n = 24)	Resected Non-adaptors (n = 9)	Gastroschisis (n = 33)
Gestational age (weeks)	39.0 ± 1.1	32 ± 5	37 ± 10	36.5 ± 1.2
Birth weight (kg)	3.02 ± 0.39	1.88 ± 1.12	2.37 ± 0.91	2.48 ± 0.53
Age at first testing (average CGA, weeks)	46.5 ± 4	49.3 ± 13.6	168 ± 110*	40 ± 18
Days of PN	0	132 ± 64	365+	62 ± 25
Intestinal pathology				
NEC	0	15 (62%)	2 (22%)	0
Atresia	0	7 (29%)	1 (11%)	0
Gastroschisis	0	(1, with atresia) (4%)	(4, all w atresia) (44%)	33
Volvulus/other	0	2 (8%)	2 (22%)	0
Small intestinal length (% expected for age/weight)	100 (predicted)	57 ± 25	28 ± 15*	100 (predicted)
Remnant Ileum (% expected for age/weight)	100	35 ± 32	8 ± 23*	100
Remnant colon (% expected for age/weight	100	98 ± 2	100	100