Emerging Therapies for Intestinal Failure – Strategies from the Distal Gut

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1. avoid exclusive or total parenteral nutrition as much as possible, and;
2. implement enteral nutrition as much as possible.

Messing and Joly, Gastro 2006;130:S43-S51.

Enteral nutrients are an important stimulus for regulating intestinal structure and function

1. Adaptive capacity of ileum > jejunum
2. Ileo-jejunal transposition induced ileal adaptation
3. Structural gradient of healthy intestine
4. Atrophy of bypassed intestine
5. Fasting impairs intestinal structure and function

How does the intestine recognize increased concentrations of specific nutrients in the intestine? What is the mechanism for the ‘workload hypothesis’?
• Products of carbohydrate and protein fermentation
• Acetate, propionate, butyrate comprise 83% of SCFAs
• Enhance structure and function in adult rodent small intestine
  • ↑ mucosal proliferation in colon, ileum and jejunum (Sakata, 1987; Kripke et al., 1989; Koruda et al., 1990)
  • ↑ transporter activity (Tappenden et al., 1997, 1998; Tappenden and McBurney, 1998)
• PN-supplemented butyrate induced intestinal adaptation in neonatal piglets (Bartholome et al., 2004)

Regardless of time, ileal villus length increased by supplemented treatments.

Experimental Design
• jugular catheterization
• nasogastric tube placement
• 80% jejunoileal resection
n = 96
24h, 3d or 7d
Ileum mucosal weight is increased by the prebiotic treatment, regardless of time:

![Graph showing increased mucosal weight with prebiotic treatment.](image1)

- Con: 0
- Pre: a
- Pro: b
- Syn: b

TXT, p=0.005; day, p<0.0001; TXT x day, p=0.163

Prebiotic treatment increases glucose transport in the jejunum:

![Graph showing increased glucose transport with prebiotic treatment.](image2)

- Con: 0
- Pre: a
- Pro: ab
- Syn: ab

TXT, p=0.042; day, p=0.092; TXT x day, p=0.484

All treatments increase glutamine transport over control in the colon:

![Graph showing increased glutamine transport with different treatments.](image3)

- Con: 0
- Pre: a
- Pro: a
- Syn: a

TXT, p=0.013; day, p=0.013; TXT x day, p=0.309
Summary from IF piglet work

Prebiotic/Synbiotic treatment increased:
- Intestinal mass
- Mucosal weight
- DNA quantity
- Glucose and glutamine transport

Glucagon-like peptide 2

- Intestinotrophic peptide secreted from enteroendocrine L-cells (Drucker et al., 1996)
- Enhances structural and functional adaptations in adult small intestine
  - Crypt-villus architecture (Drucker et al., 1996; Tsai et al., 1997)
  - Enzyme and transporter activity (Brubaker et al., 1997; Cheeseman, 1997; Kato et al., 1999)
- Prevents parenteral nutrition-induced hypoplasia in adult and neonatal small intestine (Chance et al., 1997; Burrin et al., 2000; Peterson et al., 2000)
- GATTEX, a GLP-2 analog, completed Phase III clinical trials with parenteral nutrient/fluid dependent subjects with SBS

What about humans with intestinal failure?

Intact Gastrointestinal Tract
Short-Bowel Syndrome

GLP-2 analog increases jejunal villus height and crypt depth
Design of multicenter prospective, randomized double-blind, placebo-controlled study

- 83 PN-dependent subjects with intestinal failure
- Placebo (n=16)
- GATTEX 0.05 mg/kg/d (n=35)
- GATTEX 0.10 mg/kg/d (n=32)

**Subjects**

- Optimize PN
- Stabilize PN

**Intestinal Biopsy**

- 0-8 wks
- 4-8 wks
- 24 wks

**Baseline**

- Small intestinal villous height changed -19%, +54% and +39% in the placebo, 0.05 and 0.10 groups, respectively.

**Representative change in small intestinal mucosa following 24 wks of 0.05 GATTEX administration.**

**54% of patients treated with GATTEX reduced # infusion d/wk by ≥1; response ↑ with time; wt stable**
Supplemented treatments increase plasma GLP-2 concentration at all time points.

Control < SCFA Treatments, $P = 0.007$

Taste receptors essential for sensory response to nutrients in mouth

Taste receptors throughout intestine serve as important chemosensors

Mouse antrum and α-gustducin IR

Chromogranin A IR

α-gustducin expressed in human colonic mucosa

α-gustducin IR in human colon


Rozengurt et al., AJP 2006; 291:792-802.
α-gustducin found in L-cells that secrete GLP-2

Rozengurt et al., AJP 2006; 291:792-802.

α-gustducin necessary for carbohydrate induced glucose absorption

Margolskee et al., PNAS 2007; 104:15075-15080.

Silencing taste receptors prevent butyrate from increasing GLP-2

Strategies to enhance intestinal adaptation, such as short-chain fatty acids and GLP-2 therapy, promise to reduce PNin individuals with intestinal failure.

Novel taste receptors, present throughout the intestine, may provide an important mechanism mediating these effects.
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