Emerging Therapies for Intestinal Failure – Strategies from the Distal Gut

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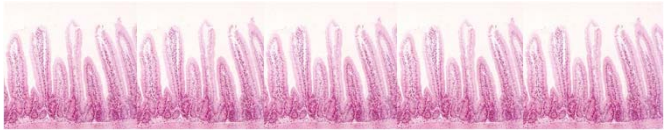
Messing's Principle's for Reducing Parenteral Nutrition Dependence

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

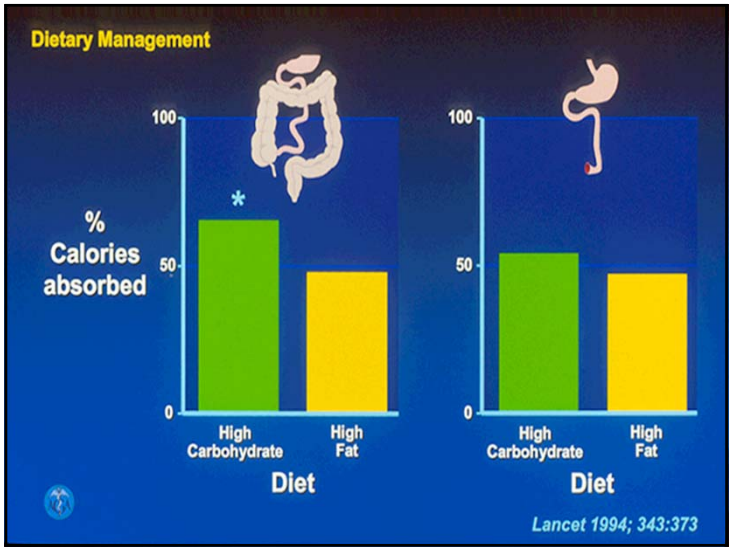
Messing and Joly, Gastro 2006;130:S43-S51.

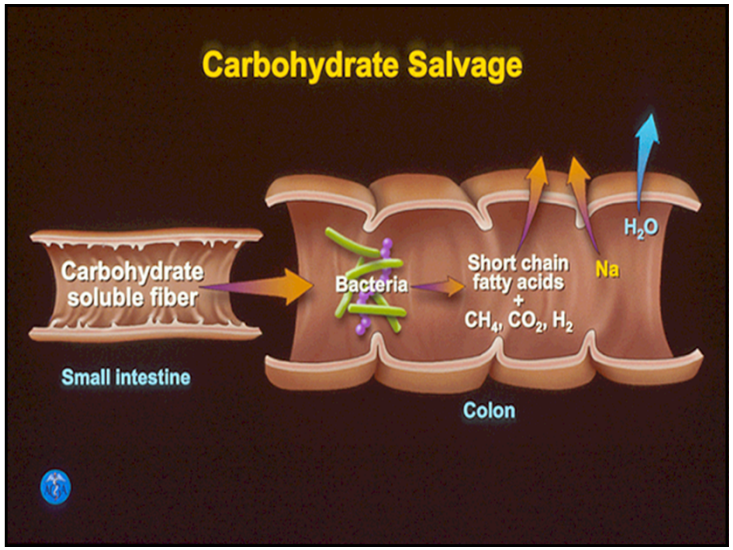


Enteral nutrients are an important stimulus for regulating intestinal structure and function

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'?

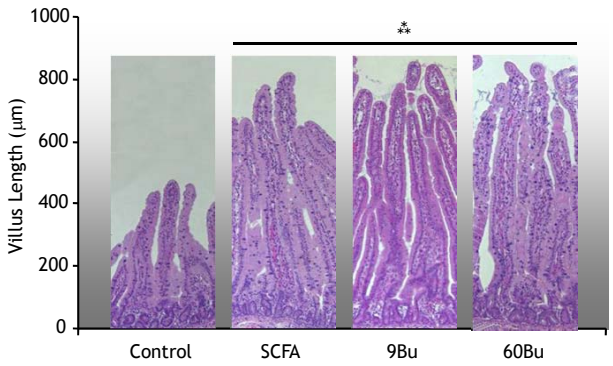




Short Chain Fatty Acids

- 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.



⁂ Ileum: Control < SCFA, $P < 0.0001$

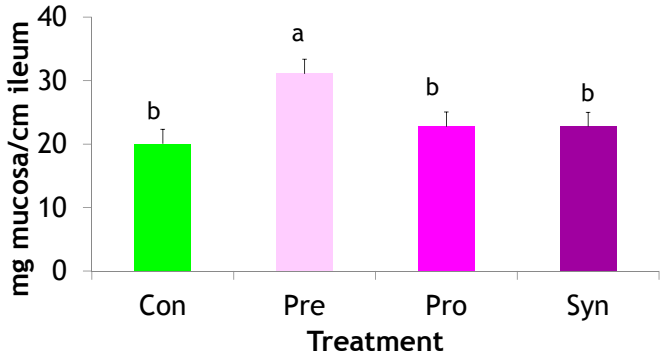
Experimental Design

- jugular catheterization
- nasogastric tube placement
- 80% jejunoileal resection

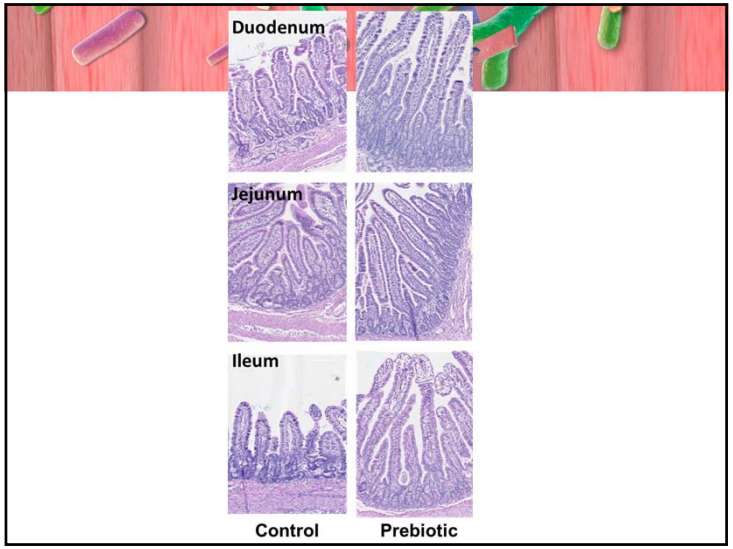
n = 96
24h, 3d or 7d

Control	Prebiotic	Probiotic	Synbiotic
20% EN/ 80% PN	10 g/kg BW FOS	$1x10^9$ CFU LGG	FOS + LGG

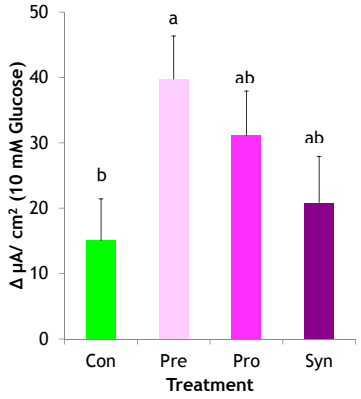
Ileum mucosal weight is increased by the prebiotic treatment, regardless of time



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

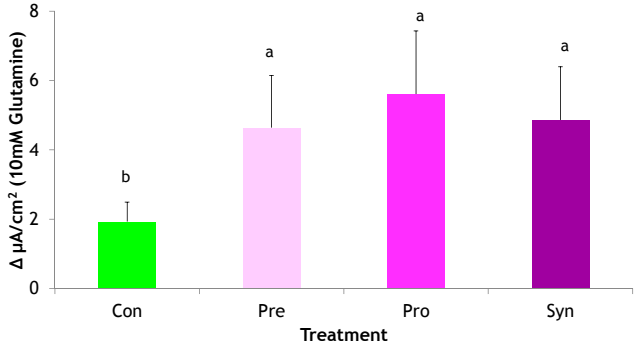


Prebiotic treatment increases glucose transport in the jejunum



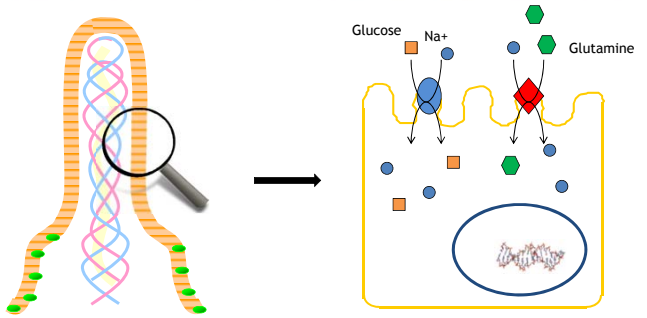
txt, p=0.042; day, p=0.092; txt x day, p=0.484

All treatments increase glutamine transport over control in the colon



txt, p=0.013; day, p=0.013; txt x day, p=0.309

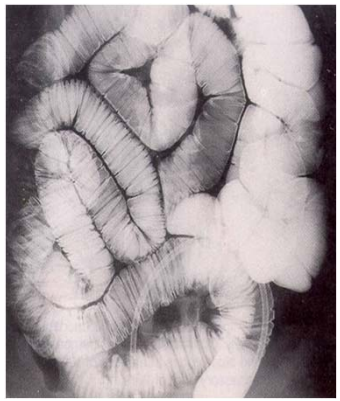
Summary from IF piglet work



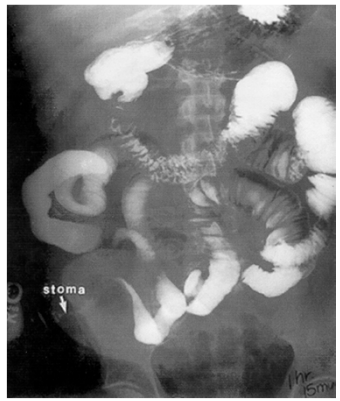
Prebiotic/Synbiotic treatment increased:

- Intestinal mass
- Mucosal weight
- DNA quantity
- Glucose and glutamine transport

What about humans with intestinal failure?



Intact Gastrointestinal Tract

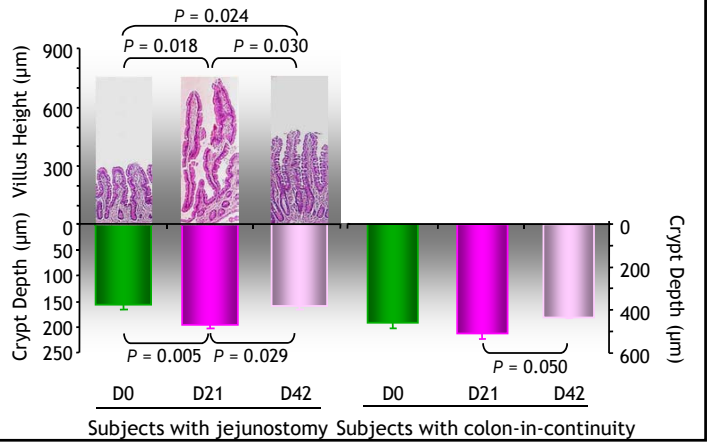


Short-Bowel Syndrome

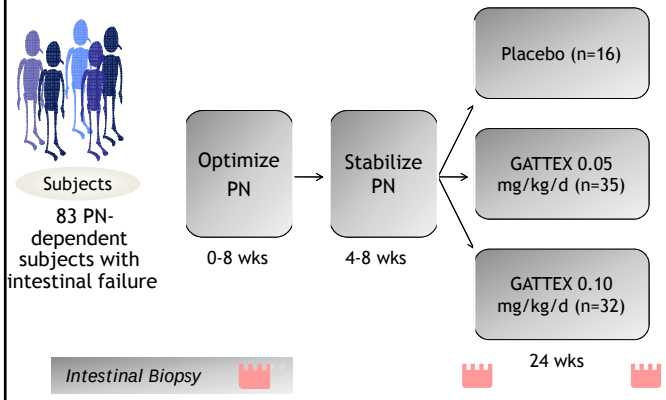
Glucagon-like peptide 2

- 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

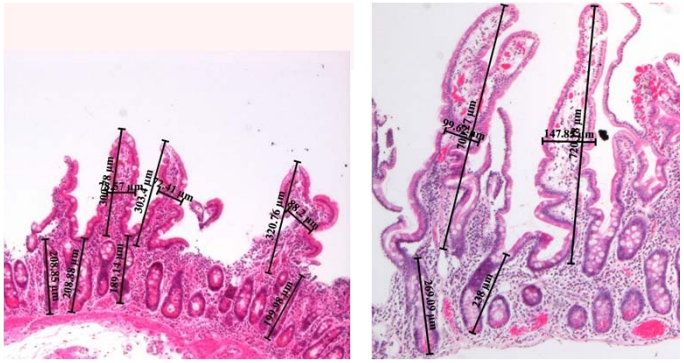
GLP-2 analog increases jejunal villus height and crypt depth



Design of multicenter prospective, randomized, double-blind, placebo-controlled study

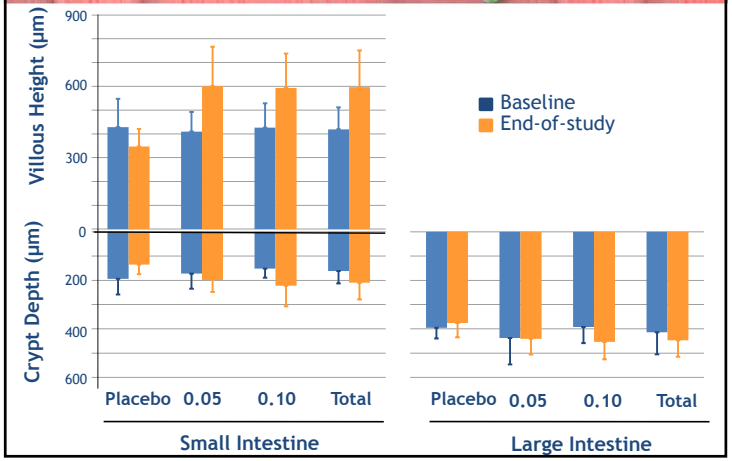


Representative change in small intestinal mucosa following 24 wks of 0.05 GATTEX administration.



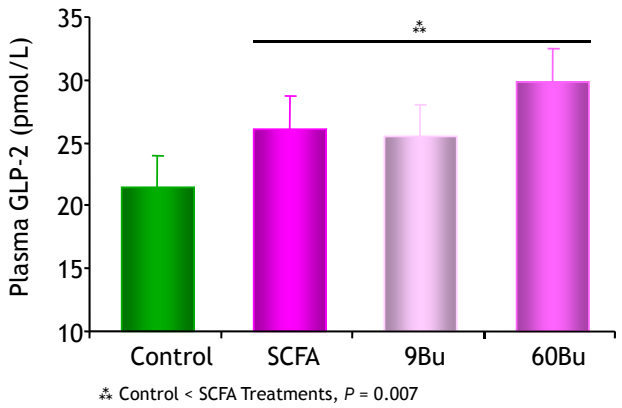
Baseline End-of-study

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



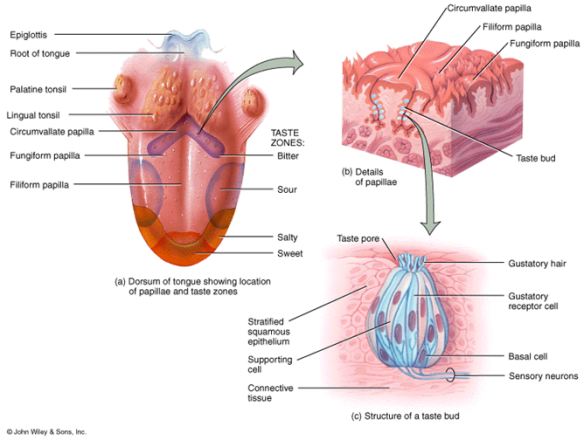
54% of patients treated with GATTEX reduced # infusion d/wk by ≥1; response ↑ with time; wt stable

Supplemented treatments increase plasma GLP-2 concentration at all time points

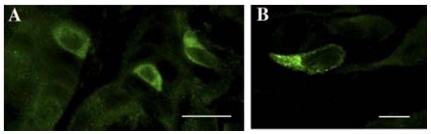


⁂ Control < SCFA Treatments, $P = 0.007$

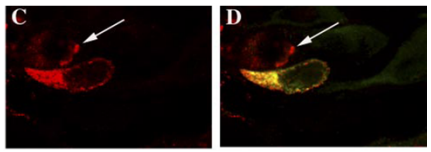
Taste receptors essential for sensory response to nutrients in mouth



Taste receptors throughout intestine serve as important chemosensors



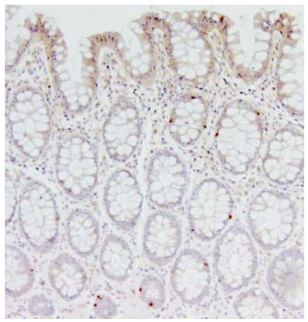
Mouse antrum α-gustducin IR



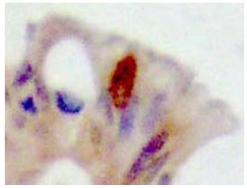
Chromogranin A IR Chromogranin A IR

Sternini C., AJP 2007;292:457-461.

α-gustducin expressed in human colonic mucosa



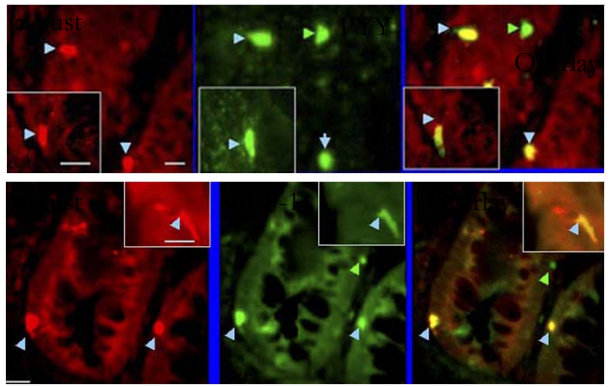
α-gustducin IR in human colon



High power x 100 view

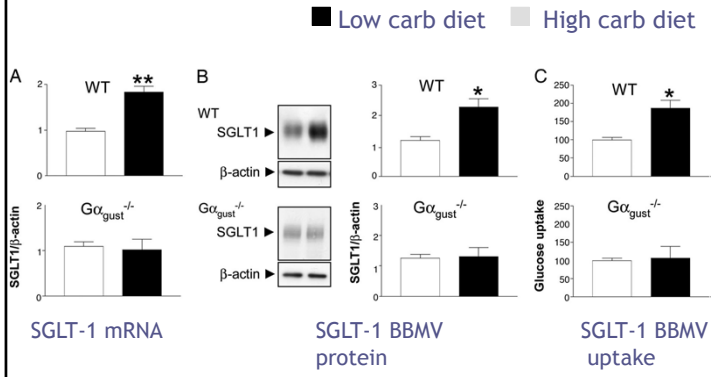
Rozengurt et al., AJP 2006; 291:792-802.

α-gustducin found in L-cells that secrete GLP-2



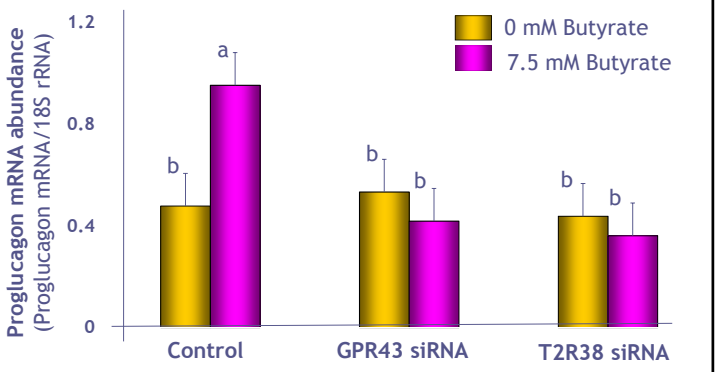
Rozengurt et al., AJP 2006; 291:792-802.

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



Take Home Message

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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