The Gut-Brain Axis…

The impact of the microbiome on brain and cognitive development

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With acknowledgements to:
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Medical Director Hospital Nutrition Support
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Our Gut Microbiome

- **Human GI tract**
  - Surface area: 300 to 400 square-meters
  - 100 trillion living bacteria
    - ~ 10 trillion cells in human body
  - Several thousand species in colon
  - Primarily made up of 4 phyla:
    - Actinobacteria
    - Firmicutes
    - Bacteroidetes
    - Proteobacteria

- **Function to:**
  - Digest “undigestable” foods
  - Produce essential cofactors and vitamins
  - Stimulate of the immune system
Newborns are exposed to pro-and prebiotics before, during, and after birth:

- **Vaginal vs C-section delivery**—
  - In the US, 1/3 by C-section
- **Breastfeeding vs Formula feeding**
  - Majority are formula-fed
  - Breastfeeding encourages bifidobacteria growth
  - Formula feeding associated with bifidobacteria, bacteroides, clostridia, streptococci
  - Breast milk composition influenced by maternal weight
  - 13 - 15% of CHO in breast milk not absorbed by infant

By ~2 years the microbiome resembles the adult bacterial profile; “blend” of bacteria based on environmental exposure.
Evolution of Our Gut Microbiome

- **Major Changes in Diet and Activity**
  - Fats, protein, fiber, food additives, sweeteners
  - Sedentary lifestyles, obesity
- **Enhanced use of immunizations & antibiotics**
- **Reduced parasitic infection**
- **Urban life in cities and concrete**
- **Reduced exposure to animals, livestock**
- **Improved refrigeration, sanitation and hygiene**
- **Introduction of solid foods, types of foods, and nutrients like iron and fatty acids impact diversity and composition of gut bacteria**
Criteria for Probiotic Designation

WHO, FAO Definition
Live microorganisms in which when administered in adequate amounts confer a health benefit on the host”

- Human origin
- Viable / hardy in human GI tract
- Acid and bile stable
- Adhesion to mucosa
- Clinically demonstrated benefit
- Safe

Most Common Commercial Probiotics
- Lactobacillus acidophilus/johnsonii/gasseri
- Lactobacillus casei
- Lactobacillus paracasei
- Lactobacillus rhamnosus
- Lactobacillus plantarum
- Lactobacillus reuteri
- Bifidobacterium animalis/lactis
- Bifidobacterium bifidum
- Bifidobacterium breve
- Bifidobacterium longum
- Bifidobacterium adolescentis
Mutually Beneficial Effects of Bacteria and Their Substrates in Humans

- Prevent infections (systemic and GI)
- Regulate local and systemic immune function
- Regulate Metabolic pathways: glycemic control, cholesterol, amino acids
- Support mucosal barrier (multiple mxs)
- Regulate appetite (leptin, ghrelin)
- Enhance nutrient utilization
- Regulate bowel motility
- Prevent neoplastic changes
- Regulate Inflammation, local and systemic

Probiotics
What is a healthy gut?

Host response
(immune system, intestine, brain-gut axis)

Shanahan F. *Gastroenterology* 2010;139:1808-12
Regional distribution of the gut microbiota

Primary site of contact
Bile and pancreatic enzymes

Peyer’s patches
Major site of adaptive immune activity

Streptococcus
Lactobacillus

Small intestine
Duodenum
Jejunum
Ileum

$10^2 - 10^4 \text{ g}^{-1}$
$10^7 - 10^9 \text{ g}^{-1}$
$< 10^4 \text{ g}^{-1}$

Stomach
Streptococcus
Lactobacillus
Staphylococcus
Veillonella

Acid challenge

Large intestine (colon)
Cecum

$10^{11} - 10^{12} \text{ g}^{-1}$

Bioreactor
Major metabolic activity
Short-chain fatty acids

Kleerebezem Ann Rev Microbiol 2009
Composition of the Human Gut Microbiota

Only 9 bacterial divisions detected but extremely diverse
Gut has strong selection for bacteria and redundancy of functions
Variety is thought to yield resilience to insults

Bäckhed Science 2005
Mechanisms of Action

Example: bacteriocins
Use of Probiotics during Pregnancy and Maternal Outcomes

- Finland N=256
- GDM defined by GTT
- 3 groups
  - Control-SOC
  - Placebo
  - Probiotics
- Results: ↓ GDM
  - Control 36%
  - Placebo 34%
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  - No change in pregnancy outcome
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- Systematic review: 189 articles
- Primary outcome
  - GDM
- Secondary outcomes
  - Pre-eclampsia
  - Inflammatory markers
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- Conclusion: Probiotics
  - ↓ GDM
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Microbial Enhancement: Use of probiotics to prevent necrotizing enterocolitis in neonates

- N=566 infants
  - Prospective RCT
  - 5 probiotic genera
    - 4 bifidobacteria, 1 lactobacillus
      - $2.0 \times 10^9$ CFU/day

- Results
  - ↓ NEC 9.8% vs 5.45 % (p<0.05)
  - ↓ Mortality 9.8 vs 6.8 % (NS)

Janvier A et al J Pediatrics 2014
Microbiota and Brain Development

- In the absence of gut microbiota, mice have:
  - substantially ↑↑ corticosterone, a stress hormone in the hypothalamus
  - ↓↓ brain-derived neurotrophic factor (BDNF) a protein that stimulates:
    - neurogenesis
    - synaptic growth
    - modulates synaptic plasticity and transmission
- Partially reversed by re-colonization with a diverse microbiota
- Suggests that active signals from the microbiota play a critical role in brain development
Microbiome required for normal gut-brain signaling

Bidirectional communication:

• ↑ Nerve Growth Factor (Lactobacillus sp)
• ↑ IL-10 (attenuates inflammation)
• Alters GABA in brain
• Required for gut Ca++ binding protein expression

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What have we learned from germ-free mice...

• When the microbiota is absent:
  – Altered sociability, decreased memory, and increased stress responses

• Bacteria produce neurotransmitters
  – norepinephrine, serotonin, dopamine,

• Certain probiotic bacteria modulate the effects of neurotransmitters
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Summary

The microbiota:

• Is established early, it’s diverse, and responds to environmental exposure

• Functions through a variety of mechanisms to enhance the integrity of the gut and the immune system

• Impacts brain and cognitive development early and throughout life

• The gut brain axis is bi-directional

• This field of study is relatively new and we have a lot to learn about the power of this system to promote health and prevent and treat disease
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- Acid challenge
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- Lactobacillus
- Staphylococcus
- Veillonella

Large intestine (colon)
- Bioreactor
- Major metabolic activity
- Short-chain fatty acids

- Bacteroides
- Bifidobacterium
- Propionibacterium
- Clostridium
- Escherichia
- Methanobrevibacter

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1. Enhancement of the epithelial barrier
   - Mucins and defensins
   - Probiotics
   - Pathogens

2. Increased adhesion to intestinal mucosa
   - Mucus

3. Inhibition of pathogen adhesion

4. Competitive exclusion of pathogenic microorganisms

5. Production of anti-microorganism substances

6. Modulation of the immune system
   - IL-10
   - TGFβ
   - Immature DC
   - Macrophage
   - Th1, Th2, Th17
   - Treg
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