The Gut-Microbiota-Brain Axis

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Dr. Hannah Holscher, PhD, RD

Assistant Professor in the Department of Food Science and Human Nutrition at the University of Illinois.

The long-range goal of her research is to develop targeted dietary interventions for disease prevention and treatment by identifying key foods and/or nutrients that can be utilized for modulation of the human gastrointestinal microbiome for health benefit.

Current clinical research in her laboratory, the Nutrition and Human Microbiome Laboratory, includes controlled feeding studies investigating the impact of specific whole foods and beverages, including, avocados, broccoli, walnuts, almonds, whole grains, and kefir on the human gastrointestinal microbiome, metabolic health, and the gut-microbiota-brain axis.
The Gut-Microbiota-Brain Axis

Hannah D. Holscher, PhD, RD
Assistant Professor
Department of Food Science and Human Nutrition
Division of Nutritional Sciences
University of Illinois
List the neurological and physiological connections that enable the bidirectional communication between the gut and the brain.

Identify lifestyle, dietary, and microbial influences on the flow and function of signaling molecules along the gut-microbiota-brain axis.

Implement dietary regimens that target the gut and gastrointestinal microbiota to improve or maintain optimal physical and mental health.
Microbiome - a collection of microbial genomes

Microbiota – a collection of microbes

- As many bacteria as host cells in human body
- 150x more bacterial genes than our human genome
GI Microbiota

**Stomach & Duodenum**
10^1– 10^2 CFU/mL
- *Helicobacter*
- *Streptococcus*

**Jejunum & Ileum**
10^4 – 10^8 CFU/mL
- *Bacteroides*
- *Streptococcus*
- *Lactobacillus*
- *Bifidobacteria*
- *Fusobacteria*

**Colon**
10^{10} – 10^{12} CFU/mL
- *Bacteroides*
- *Prevotella*
- *Faecalbacterium*
- *Ruminococcus*
- *Roseburia*
- *Clostridium*
- *Bifidobacteria*
- *Collinsella*
- *Desulfovibrio*
- *Bilophila*
- *Akkermansia*
- *Methanobrevibacter*

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Microbiota Functions

- Protective functions
- Structural functions
- Metabolic functions
  - Fermenting dietary fiber into short-chain fatty acids
  - Synthesizing vitamins
Microbiota Functions

Gut-Microbiota-Brain Communication

Bidirectional communication

- Central nervous system (brain and spinal cord)
- Autonomic nervous system (sympathetic and parasympathetic)
- Enteric nervous system (intrinsic nervous system of GI tract)
- Hypothalamic pituitary adrenal axis (HPA)
- Microbiome (collection of microorganisms and their genomes in the gut)
Major nerve of the parasympathetic division of the autonomic nervous system

Important pathway for bidirectional communication between the gut microbes and the brain

Preclinical/animal studies demonstrate that probiotic effects on brain are dependent on vagal afferent signals

- *Lactobacillus rhamnosus* directly activates vagal neurons
- Induces region-dependent alterations in GABA receptor expression in the brain and reduced stress-induced corticosterone and anxiety- and depression-like symptoms via vagus nerve signaling in mice

Vagotomized mice do not exhibit this effect

- Acetylcholine
- Noradrenaline
- Adrenaline
- Gamma-amino butyric acid (GABA)
- Serotonin
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<thead>
<tr>
<th>Neurotransmitter</th>
<th>Released By</th>
<th>Function</th>
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<tbody>
<tr>
<td>GABA</td>
<td>Central Nervous System (CNS)</td>
<td>Relaxes lower esophageal sphincter</td>
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<tr>
<td>Norepinephrine</td>
<td>CNS, spinal cord, sympathetic nerves</td>
<td>Decreases motility, increased contraction of sphincters, inhibits secretions</td>
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<tr>
<td>Acetylcholine</td>
<td>CNS, autonomic system, other tissues</td>
<td>Increases motility, relaxes sphincters, stimulates secretion</td>
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<tr>
<td>Serotonin</td>
<td>GI tract, spinal cord</td>
<td>Facilitates secretion and peristalsis</td>
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## Bacteria & Neurotransmitters

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Genus</th>
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<tr>
<td>GABA</td>
<td><em>Lactobacillus</em>,</td>
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<td><em>Bifidobacterium</em></td>
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<tr>
<td>Norepinephrine</td>
<td><em>Escherichia</em>, <em>Bacillus</em>,</td>
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<td><em>Saccharomyces</em></td>
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<tr>
<td>Acetylcholine</td>
<td><em>Lactobacillus</em></td>
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<td>Serotonin</td>
<td><em>Candida</em>, <em>Streptococcus</em>,</td>
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<tr>
<td></td>
<td><em>Escherichia</em>, <em>Enterococcus</em></td>
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</table>
Serotonin

- Biogenic amine that functions as a neurotransmitter
  - Tryptophan is precursor
  - Involved in GI secretion
  - Gut motility
  - Pain perception
  - Maintenance of mood and cognition

- 95% of serotonin is contained in the gut in the mucosa and nerve terminals of the enteric nervous system

- Alterations in serotonin transmission may underlie pathological symptoms
  - Selective serotonin reuptake inhibitors are known to modulate psychiatric and GI disorders (e.g., IBS)
Gut Hormones and Neuropeptides

Brain

Gut-brain axis

Enteric neurons
Gastrointestinal muscle

Gut immune system

Gut mucosa

Gut microbiota

Appetite and energy homeostasis
Emotionality and mood
Stress resilience and recovery
Learning and memory
Sensation and pain

Microbial factors
Gut hormones
Cytokines
Sensory neurons

Autonomic neurons
Neuroendocrine factors

Food intake, energy homeostasis
Anxiety, mood, cognition

NPY
Brain

NPY
Sympathetic neurons

Y1, Y2, Y4, Y5

NPY
Enteric neurons

Gut motility
Gut secretion
Blood flow

Mucosal immune system

Gut microbiota

Y1, Y2, Y4

Y1, Y2

PP
Pancreatic F cells

Mucosal L cells

Gut-brain axis

Brain

Enteric neurons
Gastrointestinal muscle

Gut immune system

Gut mucosa

Gut microbiota

Appetite and energy homeostasis
Emotionality and mood
Stress resilience and recovery
Learning and memory
Sensation and pain

Microbial factors
Gut hormones
Cytokines
Sensory neurons

Autonomic neurons
Neuroendocrine factors
Gut can communicate with the brain via hormonal signaling: gut peptides from enteroendocrine cells can act directly on the brain.

Germ-free studies suggest that the gut microbiota mediates and regulates the release of gut peptides.

**Gut Hormones and Neuropeptides**

- Ghrelin
- Gastrin
- Orexin
- Cholecystokinin
- Leptin
- Neuropeptide Y

**Feeding Behavior**
- Energy
- Homeostasis
- Circadian Rhythm
- Arousal
- Anxiety

Under the anaerobic conditions of the large intestine, undigested carbohydrates are fermented mainly to SCFAs:
- Acetate
- Propionate
- Butyrate
- Gases (H₂, CO₂, CH₄, and H₂S).

SCFAs have multiple effects on the host:
- Energy sources for the host
- Butyrate being consumed mainly by the colonic epithelium
- Acetate becomes available systemically

Circulating SCFAs can be carried by across the blood–brain barrier.

Microbiota-Derived Signaling

- Appetite Control
  - Peptide YY GLP-1
- Energy Expenditure
  - SCFAs
- Anti-Cancer
  - Inflammatory
- Gut Motility
  - Enteroendocrine Serotonin secretion

Intricate neurological and physiological factors enable the bidirectional communication between the gut and the brain.

Bidirectional communication with afferent and efferent signals:
- Vagus nerve
- Neuropeptides

Microbiota can influence behavior, neurophysiology, and neurochemistry.

SCFAs represent set of bacterial metabolites with potentially widespread health benefits:
- Importance of dietary fiber intake

Microbial-based therapeutics remain topic of further investigation.
List the neurological and physiological connections that enable the bidirectional communication between the gut and the brain
List the neurological and physiological connections that enable the bidirectional communication between the gut and the brain:

- Central nervous system: brain and spinal cord
- Autonomic nervous system: vagal nerve
- Enteric nervous system: GI nerves
- Microbes and their metabolites
  - SCFAs: acetate, propionate, & butyrate
  - Neurotransmitters: serotonin and GABA
- Gut Hormones: PYY
- Neuropeptides: NPY
What about diet?
Fecal communities clustered into enterotypes distinguished by levels of *Bacteroides* and *Prevotella*.

Enterotypes were associated with long-term diets:
- *Bacteroides*: protein and animal fat
- *Prevotella*: carbohydrates

Wu et al., 2011; Science
Diet can rapidly impact microbiota

- 6 male + 4 females; 21-33 years of age
- BMI 19-32 kg/m²
- Cross-over design: *ad libitum* 5-day consumption of diets composed entirely of animal or plant products

### Diet Composition

**Fiber:**
- Plant Based: 25 g per 1000 kcal
- Animal Based: 0 g per 1000 kcal

**Fat:**
- Plant: 20% kcal
- Animal: 70% kcal

**Protein:**
- Plant: 10%
- Animal: 30%
### Diets

#### Animal-based diet

**Breakfast**
- Cooked bacon
- Scrambled eggs
- Brewed coffee
- Half & half cream

**Lunch**
- Pork spare ribs
- Beef brisket

**Dinner meats**
- Salami
- Prosciutto

**Dinner cheeses**
- Blue
- Cheddar
- Caerphilly
- Camembert

**Snacks**
- Salami
- Mozzarella string cheese
- Pork rinds

#### Plant-based diet

**Breakfast**
- Granola cereal
- Jasmine rice
- Fresh onions
- Fresh tomato
- Fresh butternut squash
- Fresh garlic
- Frozen peas
- Steamed lentils
- Chili powder
- Cumin
- Coriander seed

**Lunch**
- Vegetable oil
- Salt

**Dinner**
- Jasmine rice
- Fresh cauliflower
- Fresh carrots
- Fresh onions
- Fresh green chile
- Fresh garlic
- Steamed lentils
- Frozen spinach
- Fresh tomato
- Vegetable oil
- Mustard oil
- Chili powder
- Cumin
- Coriander seed

**Snacks**
- Fresh banana
- Fresh mangoes
- Fresh papayas
- Banana chips

*David et al. Nature 2014*
Diet can rapidly impact microbiota

Plant Based Diet

Animal Based Diet

David et al. Nature 2014
Diet can rapidly impact microbiota

- Plant-based: increased short-chain fatty acids, acetate and butyrate
- Animal-based: increased branch-chain fatty acids, isovalerate and isobutyrate

Bile acids tended to increase on animal-based diet

David et al. Nature 2014
Fiber: “Non-digestible soluble and insoluble carbohydrates (≥ 3 monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (≥ 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health.”

- Different types of fibers in different types of plants
- Supplemental fibers in a range of foods
- Different botanical origins and chemical structure
  - Cellulose
  - B-glucans
  - Inulin
  - Polydextrose
  - Soluble Corn Fiber
- **Prebiotic** – a *substrate* that is selectively utilized by host microorganisms conferring a health benefit\(^1\)

- **Probiotic** – live *microorganisms* that when administered in adequate amounts confer a benefit to the host\(^2\)

- **Synbiotic**: Product that contains *both* probiotics and prebiotics

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Microbes ferment dietary fiber

Amylose: $\alpha-1,4$ glucosidic bonds

Cellulose: $\beta-1,4$ glucosidic bonds

$\beta$-Glucan: mixed $\beta-1,3$ and $\beta-1,4$ glucosidic bonds
Randomized, double-blind, placebo-controlled crossover trial with three 21-day treatment periods

Healthy adult men (n = 21)

Daily food and GI tolerance records

3 fecal specimens were collected on days 16 - 21
PDX & SCF shifted Bacteroidetes:Firmicutes Ratio

Microbiome changes with daily PDX and SCF

PC2 (9%)

PC3 (5%)

p<0.001

PC1 (10%)

SCF

PDX

NFC

Randomized, double-blind, placebo-controlled crossover trial with three 21-day treatment periods

Healthy adults (n=30)

- Control (0 g/d)
- Agave inulin (5.0 g/d)
- Agave inulin (7.5 g/d)

Daily food and GI tolerance records

3 fecal specimens were collected on days 16 - 20

Holscher, H.D. et al., Food & Function, 2014
Increased *Bifidobacterium* & decreased *Desulfovibrio*
Agave inulin: phenotypic responses

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- ![Marker](marker.png): 5.0 to 9.9% increase
- ![Marker](marker.png): 10 to 14.9% increase
- ![Marker](marker.png): > 15% increase
- ![Marker](marker.png): 0 to 0.9% decrease
- ![Marker](marker.png): 1 to 5% decrease
Identify dietary and microbial influences on the gut-microbiota-brain axis

*True or False?* Habitual diet and rapid changes in diet can influence microbial composition and microbial metabolites
Objective 2: Answer

Identify dietary and microbial influences on the gut-microbiota-brain axis

True

Both habitual diet and rapid changes in diet have been shown to influence microbial composition and microbial metabolites in adults.
Objective 2: Review

Identify dietary and microbial influences on the gut-microbiota-brain axis

Matching

1) Prebiotic  A. Microorganisms + substrates
2) Probiotic  B. Energy substrate for microbes
3) Synbiotic  C. Microorganisms
Identify dietary and microbial influences on the gut-microbiota-brain axis

1. Prebiotic (B)– a *substrate* that is selectively utilized by host microorganisms conferring a health benefit

2. Probiotic (C)– live *microorganisms* that when administered in adequate amounts confer a benefit to the host

3. Synbiotic (A): product that contains *both* probiotics and prebiotics
Identify dietary and microbial influences on the gut-microbiota-brain axis

*True or False*? All fibers and prebiotics change the composition of the microbiome in the same way.
Identify dietary and microbial influences on the gut-microbiota-brain axis

**False**

Fibers and prebiotics differentially change the composition of the microbiome. For example, SCF & PDX increased the abundances of Bacteroidetes, while agave inulin increased *Bifidobacterium*.
What about diet?

Implement dietary regimens that target the gut and gastrointestinal microbiota
Food sources of dietary fiber

- Fruits
- Vegetables
- Whole Grains
- Nuts
- Legumes
Prebiotic – a *substrate* that is selectively utilized by host microorganisms conferring a health benefit.

- **Foods**
  - Oatmeal
  - Barley
  - Onions
  - Greens
  - Berries
  - Bananas
  - Legumes

- **Supplements**
  - Tablets
  - Powders
Sources of Probiotics

Probiotic—live microorganisms that when administered in adequate amounts confer a benefit to the host

- **Foods**
  - Yogurt
  - Fermented milk drinks
  - Kefir
  - Infant formula
  - Cheese
  - Cereal

- **Supplements**
  - Capsule
  - Powder
  - Tablets
Galactooligosaccharides (GOS) 5.5 g/day

- Reduced waking salivary cortisol
  - Suppression of the neuroendocrine stress response
- Increased attentional vigilance in the processing of positive versus negative
  - interpreted as showing an early anxiolytic-like profile, where threatening stimuli are less likely to be attended to

- Reduction of anxiety like behavior and dampening of fight-or-flight response

Schmidt, K et al., Psychopharmacology (2015) 232:1793–1801
4-week intake of a 250 g of fermented milk by healthy women affected activity of brain regions that control central processing of emotion and sensation
- *Bifidobacterium animalis* subsp. *lactis* (2.5 x 10$^{10}$ CFU/day)
- *Streptococcus thermophiles* (2.4 x 10$^{9}$ CFU/day)
- *Lactobacillus bulgaricus* (2.4 x 10$^{9}$ CFU/day)
- *Lactococcus lactis* subsp. *lactis*

Beneficial effect on general signs of anxiety and depression, reduced cortisol
- *L. helveticus* and *B. longum* (3 x 10$^{9}$ CFU/day)
Neurological and physiological connections that enable the bidirectional communication between the gut and the brain

Dietary fiber, prebiotics, and probiotics impact human health and the microbiota

Much interest in understanding the complex relationships among diet, the microbiome, and health—identifying and utilizing key foods, nutrients, and microbes to modulate the microbiota for health benefit
Questions?
Connect with MFLN Nutrition & Wellness Online!

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https://vte.co1.qualtrics.com/jfe/form/SV_czEsnjD329mGgGV
Nutrition and Wellness CA
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• Thursday, September 14
• 11:00 am – 12:00 pm Eastern
• https://learn.extension.org/events/3055

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