FUNCTIONAL MEDICINE
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Emerging Science Spotlight: The Gut-Microbiome Connection

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Conflict of Interest

- Dr. Elmore declares the following conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings and honoraria
  - Dr. Elmore is a paid sales consultant for Amare Global which sells supplements to support the microbiome

Learning Objectives

- Describe the relationship between the gut microbiome and brain function (AKA the gut-brain axis).
- Discuss how alterations in the microbiome and intestinal permeability can impact anxiety, depression, and cognitive function.
- Review literature of specific probiotic strains with evidence for improvement in mood-related disorders.

True or False

- The microbiome is only comprised of bacteria.
- The microbiome is only in the gut.
- Medications have little to no impact on the microbiome.
- Dysbiosis is an unlikely cause of disease.

What is the Microbiome?

What is the Microbiome?

- The collection of all microbes, such as bacteria, fungi, viruses, and their genes, that live on and inside us
- They contribute in big ways to human health and wellness
- They protect us against pathogens, help our immune system develop, and enable us to digest food to produce energy

Where is the Microbiome?

- The entire surface of the skin
- Lining of nasal passages
- Lungs
- Urogenital tract
- Entire length of the gastrointestinal tract
  - Mouth to anus

More Bacteria than Human

- Human genome is 23,000 genes
- Human microbiome has more than 1,000,000+ genes
- The extensive distribution and concentration of the microbiome allows it to serve a sensory function for us

What are the Functions of the Microbiome?

- Metabolic
  - Virtual organ that extracts nutrients and energy from food that humans are unable to digest
  - Generates SCFAs
  - Generates vitamins and amino acids
  - Metabolizes bile acids, balancing cholesterol
  - Generates enzymes

What are the Functions of the Microbiome?

- Protective
  - Provides a barrier from gut invasion
    - Barrier: crowds out bad bacteria, yeast, virus, and parasites
    - Starve the enemy: gut microbes feed on gut nutrients so none is left for bad microbes
    - Mucous strategy: microbes can increase the thickness of mucus when inflammatory mediators attempt to cross the gut barrier
    - Bacteriocins strategy: peptides capable of killing or inactivating microbes

What are the Functions of the Microbiome?

- Trophic
  - Communication with gut lining cells and influence growth and influence gene expression
  - Education and regulation of the immune system. Early in life the bacteria determine friend from foe, later in life balances pro- and anti-inflammatory responses
  - Gut-brain axis communications which govern our response to stress, mood, behavior, and food cravings

Microbiome Builders

- Probiotic Foods
  - Apple cider vinegar, brined olives, sauerkraut, kimchi, miso, yogurt, natto
- Prebiotic Foods
  - Asparagus, garlic, bananas, jicama, sunchokes, onions, leeks
- Antioxidant Foods
  - Black tea, pomegranate, grapes, cranberries, dark chocolate, clove, peppermint

Microbiome Destroyers

- Air pollution
  - Breathing ultrafine particles alters the gut microbiome and changes lipid metabolism
  - Traffic-related air pollution alters the respiratory microbiome
- Artificial sweeteners
  - Sucralose may increase the risk of developing chronic inflammation. Acesulfame potassium induced weight gain
- Chronic stress
  - Chronic stress triggers an immune response and promoting the development of colitis
- Diet
  - A high–fat diet recruits bacteria prone to gain weight and develop obesity

Microbiome Destroyers

- Heavy metals
  - Arsenic exposure alters molecular pathways that govern DNA repair, and a healthy microbiome is protective against harm
- Infant Health
  - Birth mode, by C-section or natural birth, and what is eaten, formula or breast milk, during the first six weeks affects microbes in the gut of infants
  - The composition of the vaginal microbiome at birth has lasting effects on metabolism, immunity, and the brain
- Pesticides
  - Diazinon changed the gut microbiome of mice and may be sex specific
- Flame retardants
  - Polybrominated diphenyl ethers and polychlorinated biphenyls have a life-long impact on disease risk

Diseases and the Microbiome

Diseases Linked to the Microbiome

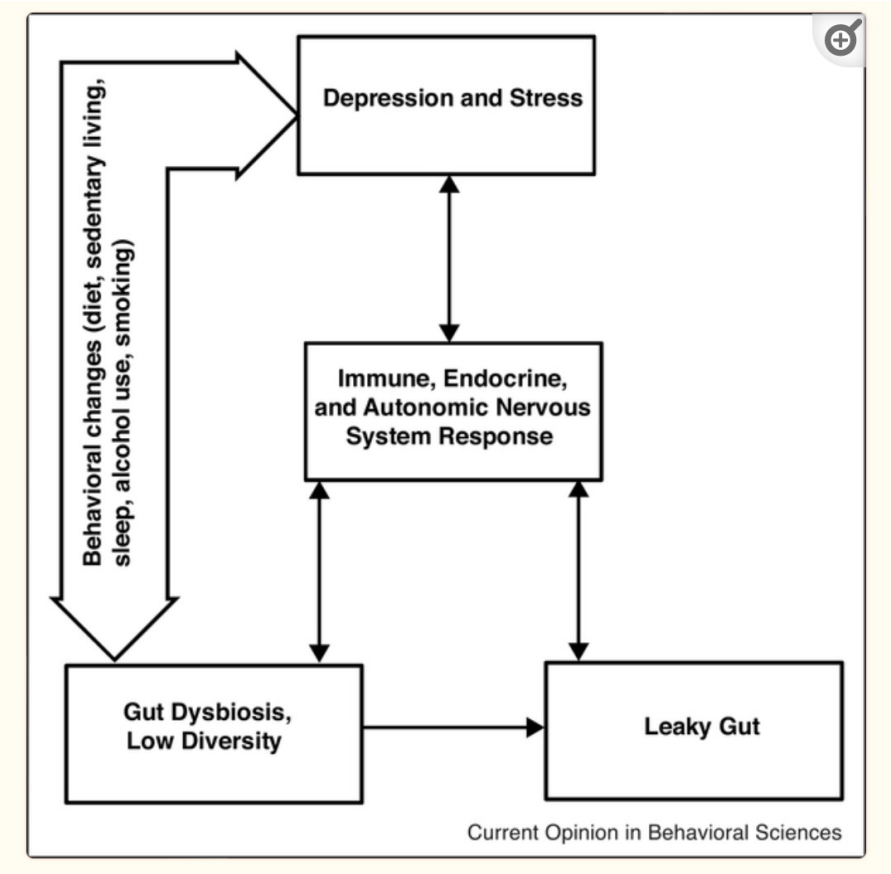
- Asthma/eczema
- Diabetes
- Obesity
- Non-alcoholic fatty liver disease
- Inflammatory bowel disease
- Irritable bowel syndrome
- Heart disease
- Mood disorders including stress, anxiety and depression

Stress

- Stress can affect health through its impact on gut bacteria
  - Stress leads to a proinflammatory state which worsens dysbiosis
  - Increased catecholamines elevate pathogenic bacteria and can make them 10,000x more infectious
  - Stressed students have lower concentrations of good bacteria
- Stress and depression can increase gut barrier permeability
  - Leaky gut further drives inflammation and stress
- Both chronic and acute stressors can shift the gut bacteria in multiple regions and habitats

1. Madison A et al. Curr Opin Behav Sci. 2019 Aug;28:105-110.

Stress and Leaky Gut



1. Madison A et al. Curr Opin Behav Sci. 2019 Aug;28:105-110.

Alterations in Microbiome

- Stress
  - Bacteroides reduced
  - Clostridium increased
    - May be due to changes in gut metabolites like phenylalanine, tryptophan, and tyrosine which are critical to the metabolism of serotonin

Depression

- Permutations in the gut microbiome composition trigger microbial lipopolysaccharides (LPS) production, activating inflammation
- Cytokines signals the vagus nerve, which links the process to the HPA axis that causes depressive effects
- GI inflammation leads to neuroinflammation
- Triggers the kynurenine pathway
- All these processes induce depression

1. Simkin DR. *Curr Psychiatry Rep.* 2019;21:93

Alterations in Microbiome

- Depression
  - *Bacteroidetes* significantly increased, whereas *Firmicutes* was markedly decreased
  - Depressive patients without IBS symptoms, the *Firmicutes/Bacteroidetes* ratio was inversely correlated with the microbiota composition profiled in patients with IBS
  - The composition and diversity of bacteria between healthy and depressed patients showed significant disparity with the depressed group showing mostly *Firmicutes*, *Bacteroides*, and *Actinobacteria* in the gut

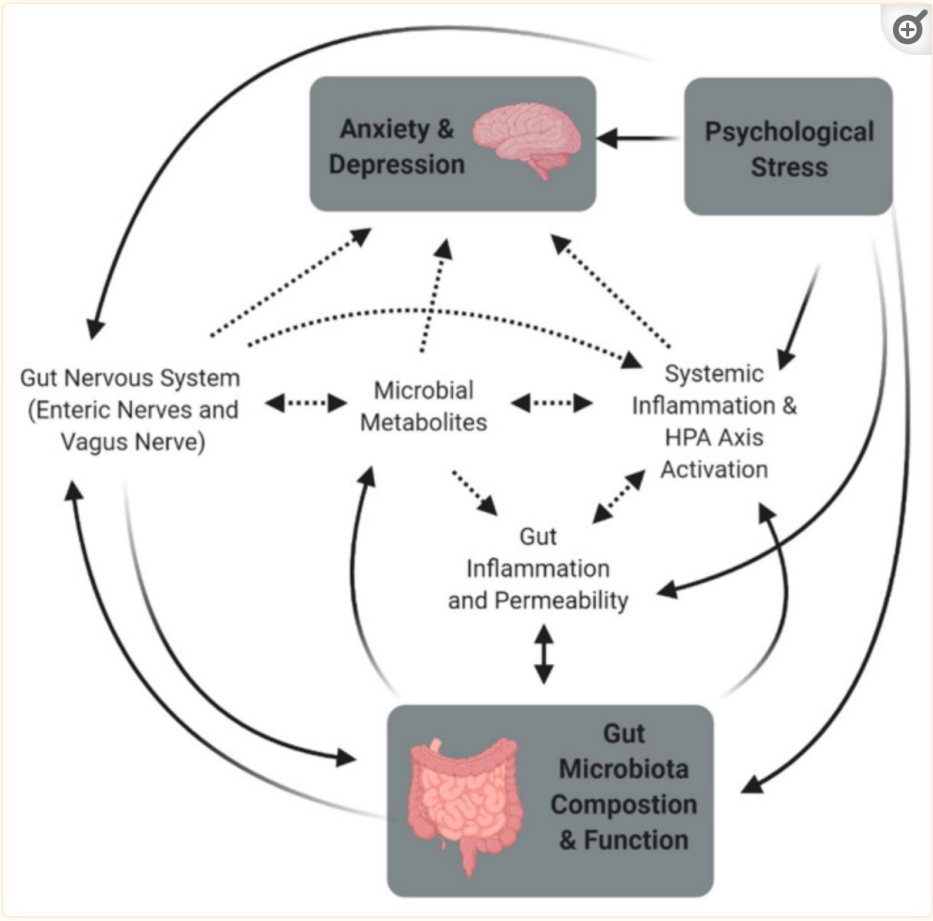
1. Limbana T et al. 2020 Aug 23;12(8):e9966.

Anxiety

- Stress-induced gut inflammation could be a key mechanism for changes in emotional behavior under stress, with the gut microbiome function promoting or decreasing gut and systemic inflammation
- Increased plasma inflammatory markers including interleukin (IL)-6 and tumor necrosis factor (TNF)-α have been found in people with anxiety

1. Bear T et al. Microorganisms. 2021 Mar 31;9(4):723.

Anxiety



1. Bear T et al. Microorganisms. 2021 Mar 31;9(4):723.

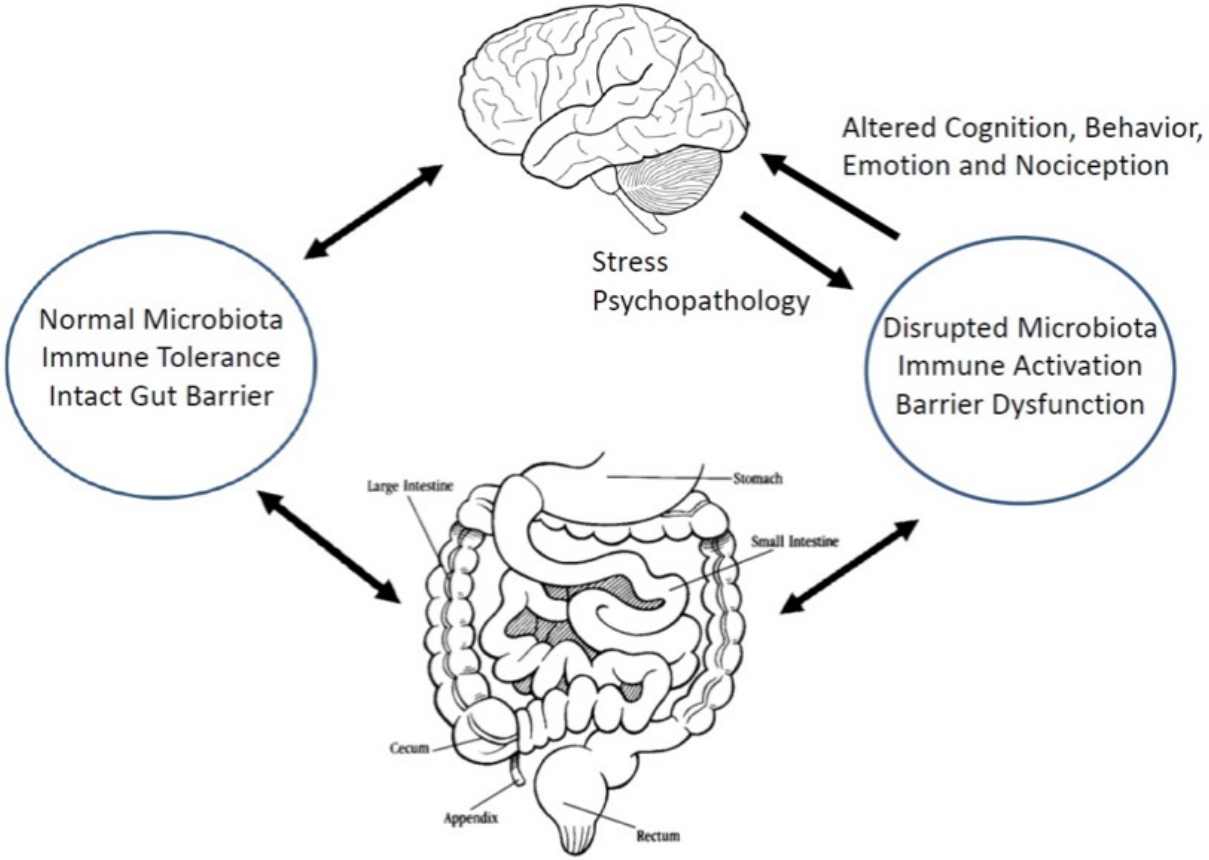
Gut-Brain-Microbiome Axis

What is the Gut-Brain-Microbiome Axis?

- A bidirectional communication between the central and the enteric nervous system
- Links emotional and cognitive centers of the brain with peripheral intestinal functions
- This interaction between microbiota and GBA is bidirectional
  - Gut-microbiota to brain
  - Brain to gut-microbiota
  - Neural, endocrine, immune, and humoral links.
- Dysbiosis is associated with CNS disorders including anxiety, depression, autism and GI disorders like irritable bowel syndrome

1. Carabotti M. Ann Gastroenterol. 2015 Apr-Jun;28(2):203-209.

What is the Gut-Brain-Microbiome Axis?



Quigley EMM. Journal of Clinical Medicine. 2018; 7(1):6.

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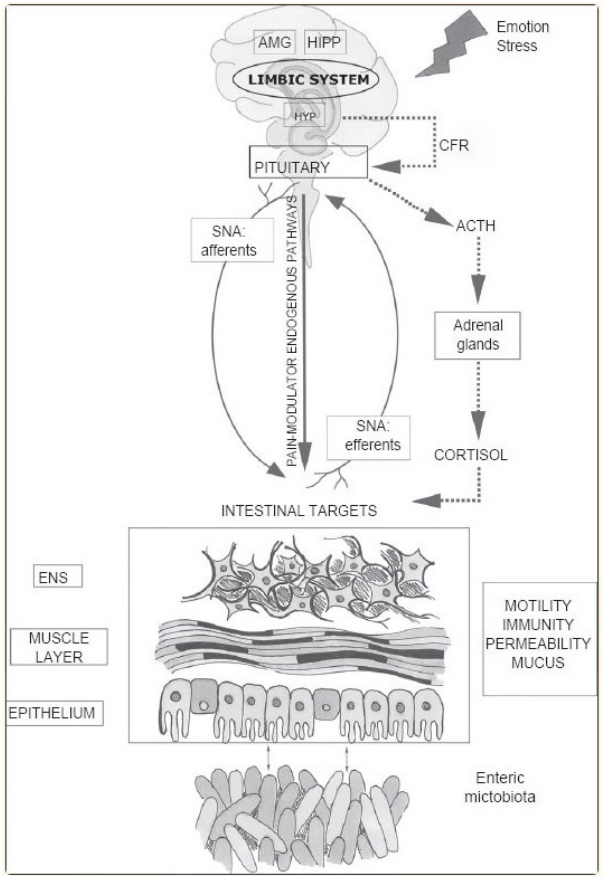
What is the Gut-Brain-Microbiome Axis?



1. Carabotti M. Ann Gastroenterol. 2015 Apr-Jun;28(2):203-209.

Multiple Choice Question

- The Gut-Brain-Microbiome Axis is:
  A. Unidirectional with the gut only talking to the brain
  B. Exclusively communicates via the immune system
  C. Not manipulable, once it is set in infancy, it is set
  D. A complex communication network that informs our metabolic, immune, and

Medications and the Microbiome

Medications that Change the Microbiome

- Any medicine that causes constipation or diarrhea.
  - Opioids, calcium, laxatives, and more.
- Any medicine that reduces stomach acid
  - PPIs, H_2RAs, antacids
- Any medicine that disrupts blood homeostasis
  - Aspirin, ibuprofen, anticoagulants, other antiplatelet medicines

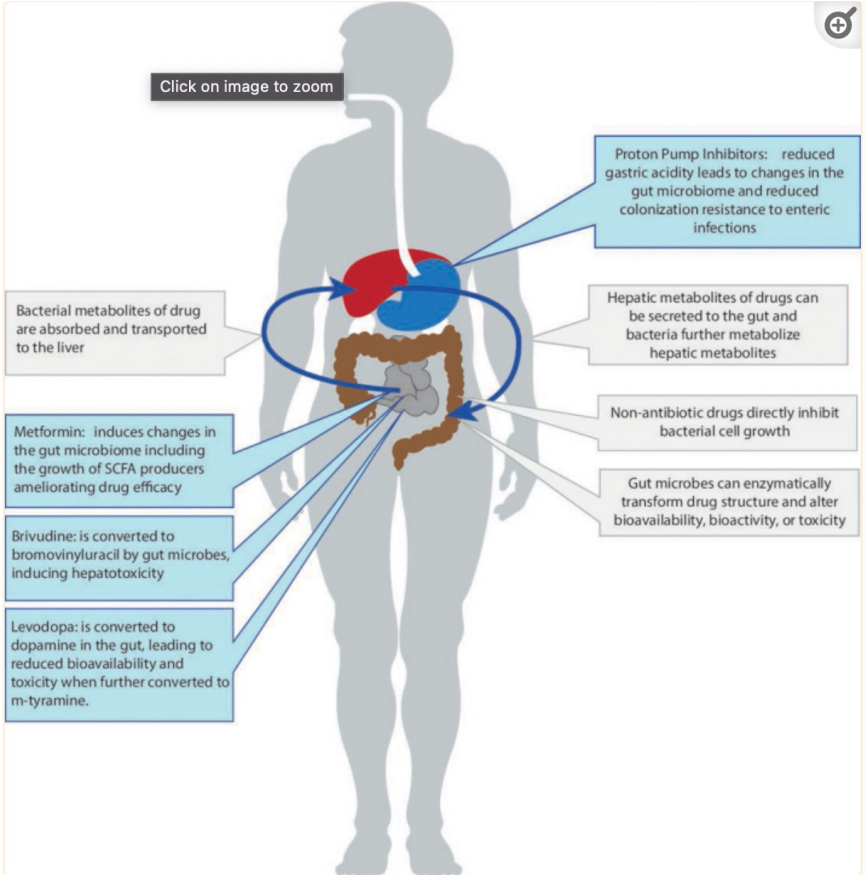
1. Weersma RK et al. Gut. 2020 Aug;69(8):1510-1519.

Medications that Change the Microbiome

- All antidepressants
- All statins
- All antihistamines
- All oral contraceptives
- Beta blockers, ACE-I, ARBs, and alpha blockers.
- Metformin
- Antibiotics

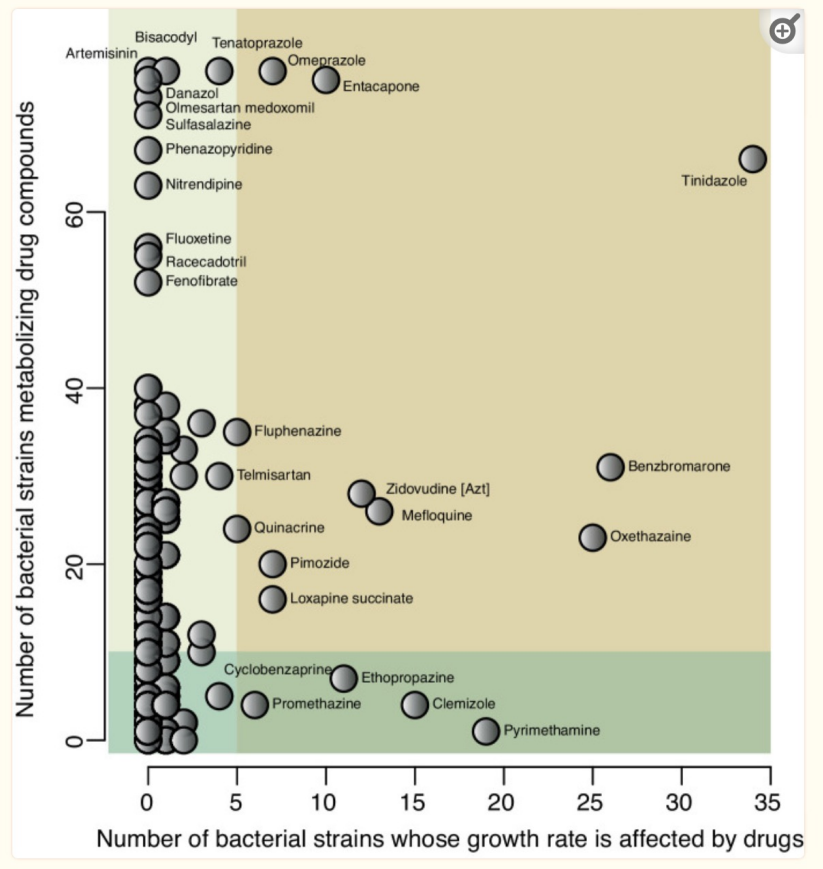
1. Weersma RK, Gut. 2020 Aug;69(8):1510-1519.

Medications and the Microbiome



1. Weersma RK, Gut. 2020 Aug;69(8):1510-1519.

Bidirectional Impact of Medications



1. Weersma RK, Gut. 2020 Aug;69(8):1510-1519.

Medications, Microbiome and Depression

- Medication Induced Depression
  - Fluoroquinolones
- Antidepressant Antibiotics
  - β-lactams and tetracyclines

Medications, Microbiome and Anxiety

- Antibiotic Induced Anxiety
  - Fluoroquinolones
- Antibiotics administered during times of stress enhance bacterial adherence to the lumen of the gut
  - Increased *Clostridia* species, and reduces *verrocobactera*, *Lactobacillus*, and *Enterococcus*

1. Bear T et al. Microorganisms. 2021 Mar 31;9(4):723.

True or False

- Medications are very highly unlikely to alter the microbiome.

Finding the Right Probiotic Supplement

Why is Strain Specificity Important?

- Most probiotics only list the genus and species of bacteria, not the strain
  - Lactobacillus acidophilus
  - Lactobacillus acidophilus La-14
- Some general effects of bacteria are well studied
  - Acid and SFCA production, normalization of microbiota diversity, competitive exclusion of pathogens
- Species-level effects
  - Vitamin synthesis, bile salt metabolism, gut barrier reinforcement

1. Ducrotte, P et al. World J Gastroenterol, 2012. 18(30): p. 4012-8.
2. Niedzielin, K. Eu J Gastroenterol Hepatol, 2001. 13: p. 1143-1147.
3. Ligaarden, S.C., et al., BMC Gastroenterol, 2010. 10: p. 16.

Why is Strain Specificity Important?

- Strain-specific effects
  - Neurological, endocrinological, immunological effects, production of specific bioactives
- Strains of bacteria within the same species can have significantly different actions, properties and characteristics
  - *Lactobacillus plantarum* 299v reduces IBS symptoms
  - *L. plantarum* MF1298 worsens IBS symptoms

1. Ducrotte, P et al. World J Gastroenterol, 2012. 18(30): p. 4012-8.
2. Niedzielin, K. Eu J Gastroenterol Hepatol, 2001. 13: p. 1143-1147.
3. Ligaarden, S.C., et al., BMC Gastroenterol, 2010. 10: p. 16.

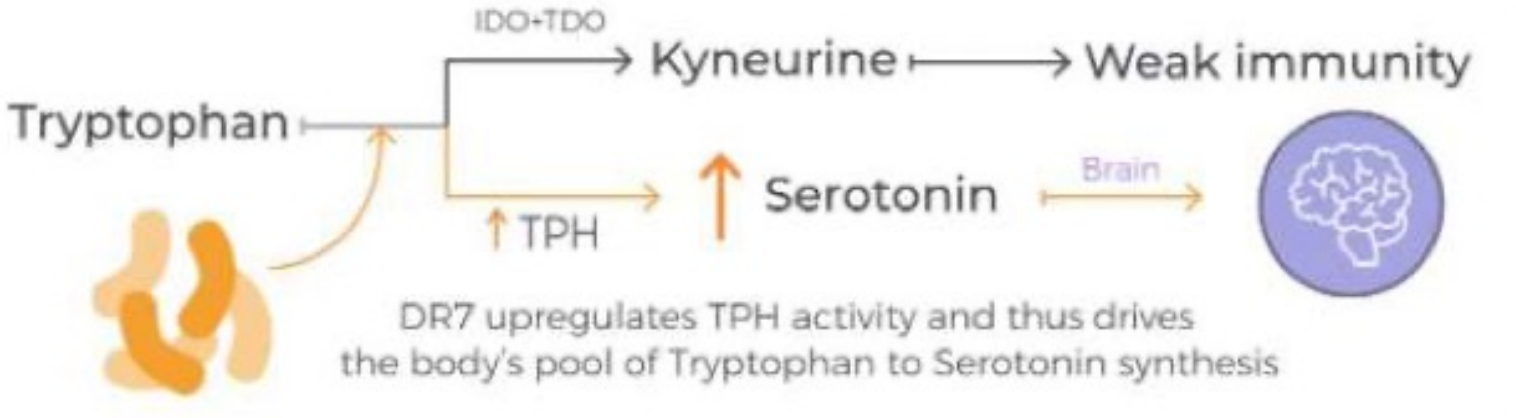
Specific Bacteria

- *Lactobacillus rhamnosus R0011*
  - Reduces stress by lowering cortisol exposure and improves GABA neurotransmission.
- *Bifidobacterium longum R0175*
  - Enhances calmness by decreasing anxiety indices and improves cognitive function.
- *Lactobacillus helveticus R0052*
  - Improves mood by decreasing neuro-inflammation and increasing serotonin.

1. Messaoudi et al. Br J Nutr. 2011 Mar;105(5):755-64.
2. Bercik et al. Gastroenterology. 2010 Dec;139(6):2102-2112.
3. Savignac et al. Neurogastroenterol Motil. 2014

Specific Bacteria

- *Lactobacillus plantarum* DR7
  - Optimizes serotonin pathways, increases dopamine, lowers cortisol, and lowers stress



1. Guoxia et al. DOI: 10.3390/ijms21134608
2. Chong HX et al. Benef Microbes. 2019 Apr 19;10(4):355-373
3. Zaydi et al. Benef Microbes: 11 (8)- Pages: 753 - 766.

Specific Bacteria

- *Lactobacillus plantarum* DR7
  - DR7 (1×10^9 cfu/day) for 12 weeks reduced symptoms of stress (*P*=0.024), anxiety (*P*=0.001), and total psychological scores (*P*=0.022) in 8 weeks
  - Plasma cortisol level was reduced compared to the placebo
  - Pro-inflammatory cytokines were reduced, and anti-inflammatory cytokines were increased (*P*<0.05).
  - DR7 better improved cognitive and memory functions in adults >30 years, such as basic attention, emotional cognition, and associate learning (*P*<0.05), compared to the placebo and young adults <30 years

1. Chong HX et al. Benef Microbes. 2019 Apr 19;10(4):355-373

Specific Bacteria

- *Bifidobacterium longum* 1714
  - Decreases stress-induced hyperthermia and produces antidepressant-like effects
  - Lowers anxiety equivalent to escitalopram
- *B. breve* 1205
  - Lowers anxiety equivalent to escitalopram

1. Savignac HM et al. Neurogastroenterol Motil. 2014 Nov;26(11):1615-27

Specific Bacteria

- *Lactobaccilus rhamnosus JB-1*
  - Aleviates depression and anxiety
  - Reduces corticosterone
- *Lactobacillus reuteri ATCC 23272*
  - Prevents depression
  - Reduces kynurenine pathway
  - Blocks production of ROS
- *Bifidobacterium infantis 35624*
  - Reduces depressive symptoms

1. Bear T et al. Microorganisms. 2021 Mar 31;9(4):723.

Specific Bacteria

- *Lactobacillus helveticus* ns8
  - Maintains BDNF in hippocampus
  - Prevents stress-induced changes in behavior and increases in corticosterone and IL-10

1. Bear T et al. Microorganisms. 2021 Mar 31;9(4):723.

Shelf Life

- In general, probiotics are shelf stable for up to 18 months to 2 years when stored below 79 degrees F
- Some studies suggest refrigeration can extend expiration date
- Heat can degrade probiotics, do not mix in hot foods/beverages
- Viability of live microorganisms varies depending on probiotic strain and CFU
- Formulation manipulations further increase shelf stability
  - Microencapsulation
  - Freeze drying

Refrigeration

- Different bacteria are more heat stable than others
- Refrigeration is not required
  - *Saccharomyces boulardii*
  - *Bacillus coagulans*
  - *Bacillus subtilis*
- Defer to label instructions to determine whether or not refrigeration is needed

Emerging Heat-Kiled Data

- It was once thought that bacteria had to be active in order to have beneficial effect
- Now, heat-killed probiotics are known to have physiological benefit
  - Dermatologic conditions
  - Allergies
  - Bloating
  - Infantile colic
  - Resilience to GI infection

Piqué N, Int J Mol Sci. 2019 May 23;20(10):2534.

Survivability in the GI Tract

- Survival rates estimated at 20-40% for selected strains, the main obstacles to survival being gastric acidity and the action of bile salts
- Coadministration with prebiotics may improve survivability
- Increased CFUs
- Administration in foods may be more effective than capsules

Saxelin M, Int J Food Microbiol. 2010 Dec 15;144(2):293-300.

Multiple Choice Question

- When selecting a probiotic,
  A. Strain-specificity is very important
  B. Only choose supplements in the refrigerator
  C. Ignore the CFUs
  D. There is no benefit of heat-killed species

Initiating Probiotics

- Probiotics are not benign and people do have side effects, especially at initiation
  - Bloating
  - Gas
  - Abdominal discomfort
- May be worsened in people with pre-existing SIBO
  - May initiate a 10-day course of digestive enzymes with 2-3 days of an herbal laxative like cascara, slippery elm, or aloe
  - Consider treatment with antibiotics/prokinetics
- Probiotic therapy should not be initiated in people who are critically ill

Didari T et al. Expert Opinion on Drug Safety 2014 13:2, 227-239

Probiotics Alone are Not Enough

- Implement the Entire 5R Protocol
  - Remove gut triggers
  - Repopulate the gut with pre- and probiotics
  - Replace vitamins, minerals, and enzymes that have been lost
  - Repair the lining of the gut
    - Vitamin D_3, omega-3 fatty acids, butyrate, L-theanine
  - Rebalance attitude and stress response

Take-Aways

1. The gut-brain-microbiota axis has major influence on the pathophysiology of anxiety, stress and depression.
2. Strain specific bacteria can modulate neurotransmitter and hormones that influence anxiety, stress and depression
3. Alterations

Questions?

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