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The Influences of the Gut Microbiome on Behavior

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EXPERIENCE:
Clinical experience in the adult inpatient acute-care and outpatient settings, specifically with surgical oncology and solid organ transplant populations, as well as the surgical intensive care unit.

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KATE FARMS CONTINUING EDUCATION PROGRAM

Presentation content: "The Influences of the Gut Microbiome on Behavior" broadens the understanding of the connections between the gut-brain axis and nutritional interventions, including diet, probiotics and prebiotics.

- The connection between the gut microbiome and human behavior – specifically, that how a person eats influences his/her gut microbiome enough to influence development and/or symptoms of depression, anxiety, ADHD and/or ASD
- Nutritional changes that can improve the microbiome, and subsequently improve behaviors/mental health

CPEUs hours approved: 1.0
CPEU levels: 1 and 2
Approved by: Academy of Nutrition and Dietetics

Performance Indicators/Learning Objectives
10.4.4 Makes recommendations for the appropriate use of vitamin and mineral supplementation in the management of health and disease.
8.2.3 Implements individualized services to reflect customer-centered approach as it pertains to the customers physical, social, cultural, institutional and economic environment.
8.3.3 Takes action to address deficiencies to enhance practice.
8.3.7 Integrates new knowledge and skills into practice.

Learning Need Codes
4040: Disease prevention
5220: Gastrointestinal disorders
5300: Neurological: stroke, Alzheimer's, dementia, Parkinson's spinal cord injuries
5320: Psychiatric disorders, anxiety

AGENDA

What we absorb and assimilate

versus

what we eat or consume

INTRODUCTION

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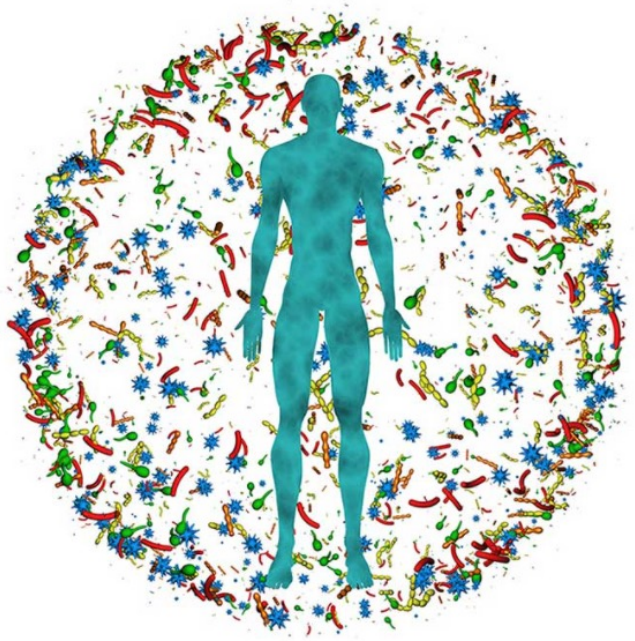
MICROBIOME

The microbiome is defined as the collective genomes of the microbes (composed of bacteria, bacteriophage, fungi, protozoa and viruses) that live inside and on the human body. We have about 10 times as many microbial cells as human cells.

– **HUMAN GENOME PROJECT**



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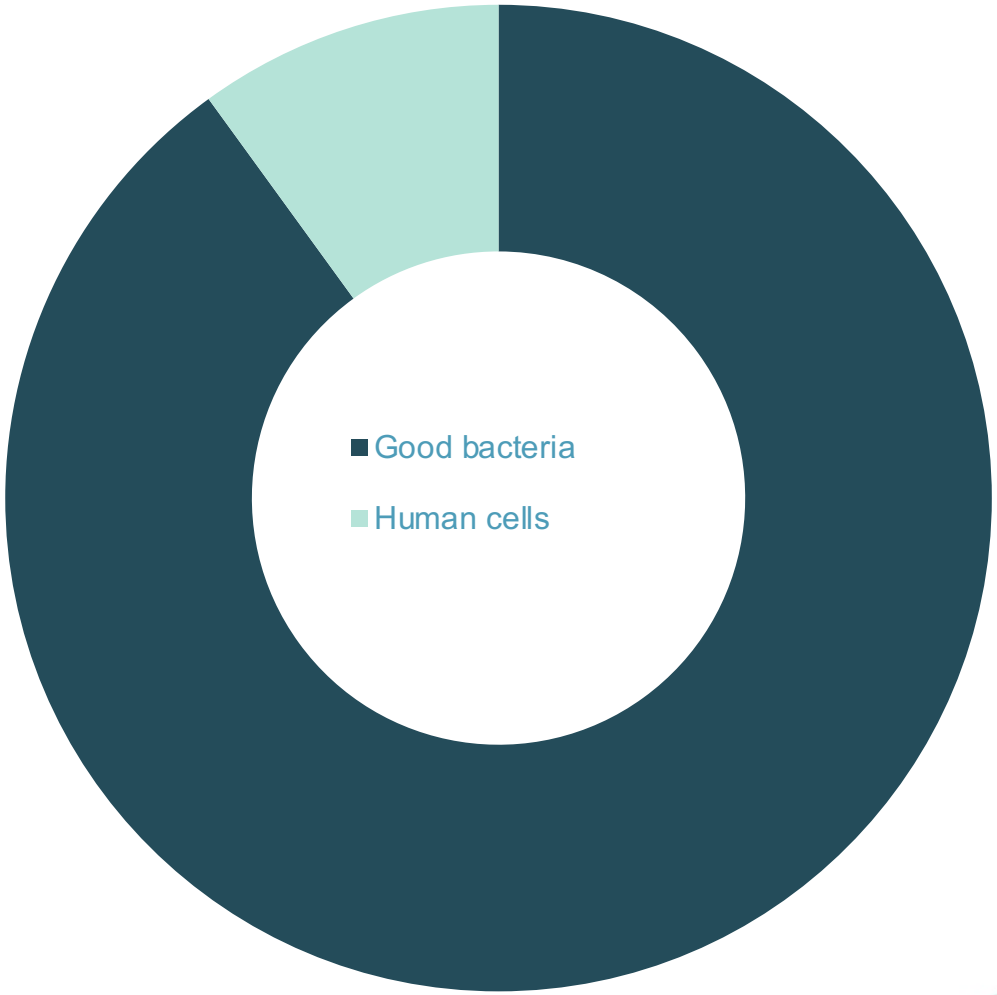
MICROBIOME

90% of the cells in the human body are commensal bacteria or “good bacteria”; only 10% are human eukaryotic cells



MICROBIOME

1900s: Researchers link anecdotal reports of behavior to intestinal health

> “It is far from our mind to conceive that all mental health conditions have the same etiological factor, but we feel justified in recognizing the existence of cases of mental disorders which have as a basic etiological factor a toxic condition arising in the gastrointestinal tract.”

ARMANDO FERRARO (CLINICAL PSYCHIATRIST), JOSEPH E. KILMAN (NEW YORK PSYCHIATRIC INSTITUTE)

BACKGROUND

Commensal bacteria: our anti-inflammatory, or “good” bacteria

- Make short-chain fatty acids (SCFA) in colon
  - Bioactive metabolic products that help to fortify the intestinal barrier by influencing expression of tight junction proteins
- Assist with nutrient metabolism
  - Example: K1 --> K2 conversion

DYSBIOSIS

> "A relationship of non-acute host-microorganism interaction that adversely affects the human host [for which subtypes] can be distinguished based on location: *gastrointestinal, orodental, sinorespiratory, genitourinary, dermal, or environmental*."

CONSEQUENCES OF GUT DYSBIOSIS

- Decreased production of short-chain fatty acids (SCFA)
  - SCFA made from fermentation of dietary insoluble fiber in the colon
  - Decrease in SCFA linked to cardiovascular disease and other adverse health outcomes
- Increased intestinal pathogen susceptibility
- Overgrowth of clostridium difficile (C.Diff)
- Decreased production of beneficial bacterial responsible for immune system development
- Improper nutrient metabolism

Wong et al., 2006

IDEAL “HEALTHY” GUT MICROBIOME

- More commensal bacteria, less harmful bacteria

- Increased diversity within archaeal phylum --> all players on the team accounted for
  - Primary “players” in a healthy human microbiome (all have some variation)
    - Firmicutes phyla
    - Bacteroidetes phyla
    - Actinobacteria phyla (bifidobacteria, lactobacilli)
    - Proteobacteria phyla
    - Fusobacteria phyla
    - Verrucomicrobia phyla
    - Cyanobacteria phyla

Alou et al., 2016

INFLUENCES OF THE GUT MICROBIOME COMPOSITION

- Diet: Western, or “SAD”
- Environmental exposure to toxins
- Overuse of antibiotics
- Probiotics/prebiotics
- Stress
  - Suppresses “good” bacteria: bifidobacteria, lactobacilli
  - Increases “bad” bacteria: bacteriodes fragilis

Intestinal Permeability

INTESTINAL PERMEABILITY OR 'LEAKY GUT'

Intestinal permeability	Defined as a functional feature of the intestinal barrier at given sites, measurable by analyzing flux rates across the intestinal wall as a whole, or across wall components of defined molecules that are largely inert during the process and that can be adequately measured in these settings.
Normal intestinal permeability	Defined as a stable permeability found in healthy individuals with no signs of intoxication, inflammation or impaired intestinal functions.
Impaired intestinal permeability	Defined as a disturbed permeability being non-transiently changed compared to the normal permeability, leading to a loss of intestinal homeostasis, functional impairments and disease.

 **All definitions from Bischoff et al., 2014*

INFLUENCES OF INCREASED INTESTINAL PERMEABILITY

- **Change in diet** → alteration of gut microbiome → gradual immune response and activation → increases inflammation → increases intestinal permeability

- **External/environmental stress via CRF** (corticotrophin releasing factor) and CRF receptors promote gradual immune response and activation
  - Increase in inflammation
  - CNS response to stress: release of neurochemicals/peptides that can result in impairment of the immune system

Neuman et al 2015

MARKERS OF INTESTINAL PERMEABILITY

- "Sugar" challenge tests (urine)
  - Lactulose/mannitol
  - Sucrose
  - Sucralose
- Serum markers
  - Zonulin (Small intestine)
  - Citrulline (Small intestine)
  - D-Lactate (Entire intestine)
- Fecal markers
  - Calprotectin (non-specific for inflammation)
  - Zonulin

Kelly et al., 2015

QUESTIONS THAT ARISE

How is all this connected?

How does this relate
to human behavior?

AGENDA

01 INTRODUCTION

02 **GUT-BRAIN AXIS**

GUT – BRAIN AXIS CONNECTION

What is it?

- Bidirectional communication between the brain (central nervous system) and the gut
- Connection first shown with rodent models, and comorbidities between GI disorders and mood disorders in humans

50%

of those with IBS have a mood disorder, such as depression/anxiety

Whitehead et al, 2002

GUT – BRAIN AXIS CONNECTION

Mechanisms not fully understood; however, they are hypothesized to be:

V.E.I.N.

- » Vagus nerve connection
- » Endocrine or HPA axis (associated with stress)
- » Immune system development/modulation
- » Neurotransmitter production

Whitehead et al, 2002

GUT – BRAIN AXIS CONNECTION

V: Vagus nerve stimulation

- Vagus nerve connects from gut lining up to brain stem
- 200-600 million neurons connect gut to brain via Vagus nerve *Bravo et al, 2012*

Illustration via this study: Two groups of mice considered to have "depression-like symptoms"- one group with intact vagus nerve and one with severed vagus nerve; both groups treated with Lactobacillus rhamnosus.

The group of mice with the **intact vagus nerve** had **improved** depression-like symptoms compared to the group of mice who had a severed vagus nerve.

Wang et al, 2016

GUT – BRAIN AXIS CONNECTION

E: Endocrine communication via HPA axis (hypothalamus-pituitary-adrenal): stress-related

Stressor → hypothalamus releases corticotrophin-releasing hormone → pituitary →pituitary releases ACTH → adrenals make cortisol → high cortisol may increase intestinal permeability *(Kelly et al, 2015)*

- In mice: Lactobacillus helveticus R0052 and bifidobacterium longum R0175 improved HPA changes induced by stress, and restored tight junctions in intestine

- In mice: Lactobacillus farciminis supplementation; suppressed changes to intestinal permeability caused by stress

Wang et al, 2016

GUT – BRAIN AXIS CONNECTION

E: Endocrine-Stress Pathway in Humans

Mothers who reported more stress during pregnancy, while also having increased salivary cortisol, had infants with:

- Decreased lactic acid producing bacteria (Lactobacillus) and bifidobacteria with an increase in proteobacteria
- These infants also had an increase in allergies & increase in negative GI symptoms

Zylmanse at al, 2015

GUT – BRAIN AXIS CONNECTION

I: Immune System

- Commensal bacteria can help to decrease pro-inflammatory cytokines, thereby helping to reduce inflammation.

- Reduction of inflammatory cytokines can help to reduce HPA activity.

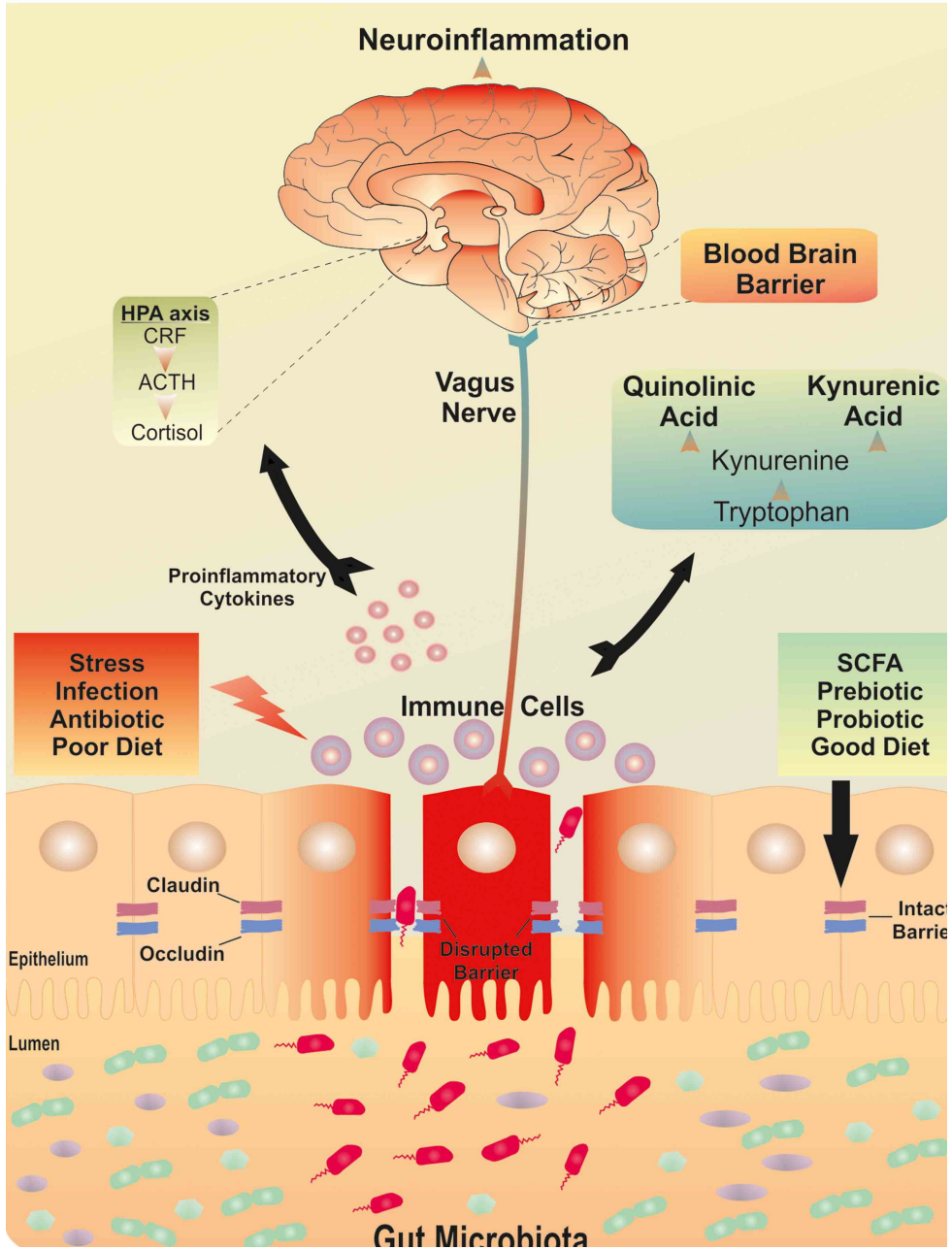
GUT – BRAIN AXIS CONNECTION

N: Neurotransmitter Production by Gut Bacteria

Tryptophan is converted to serotonin or kynurenic acid:

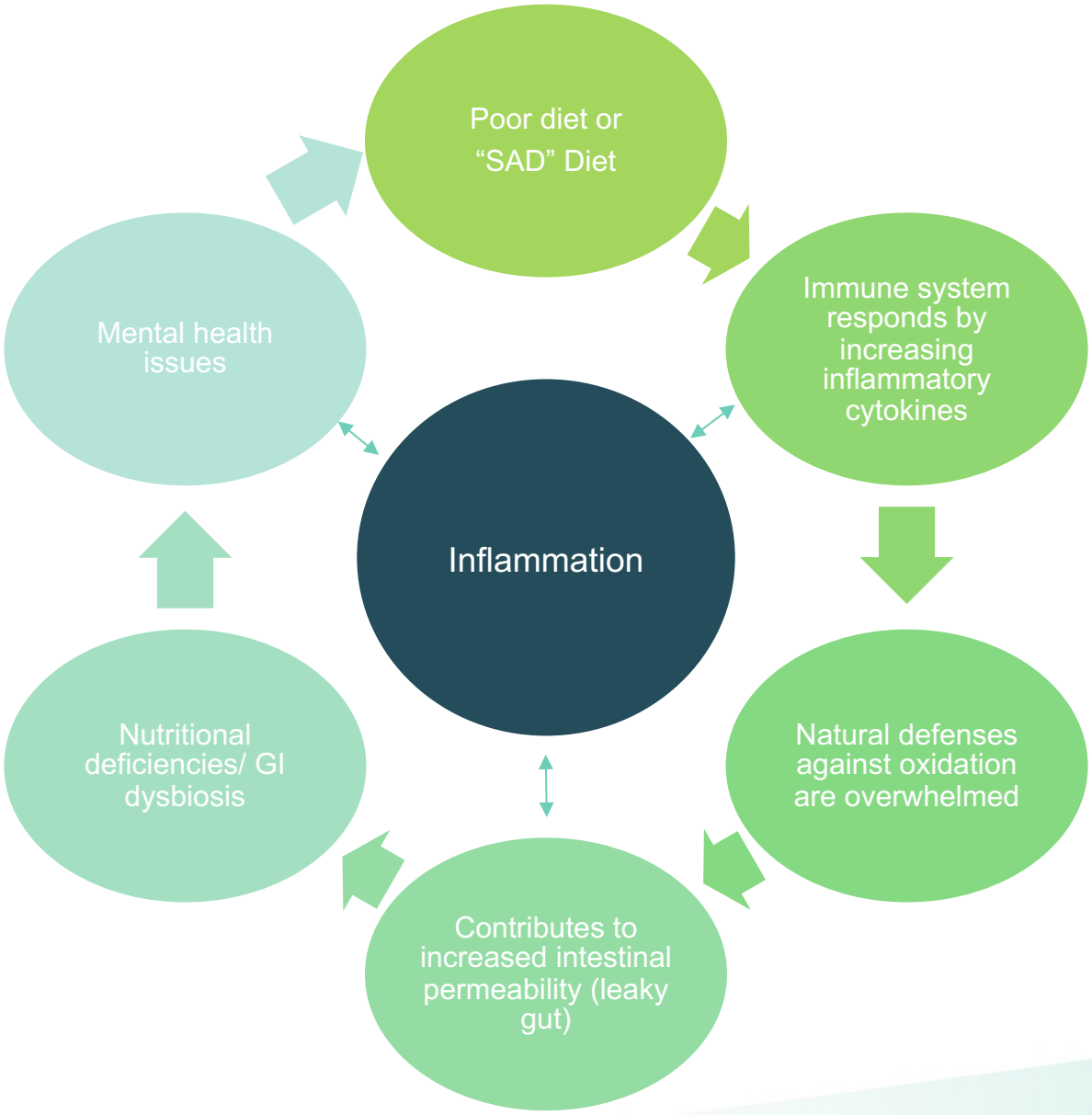
- Pathogenic bacteria can produce kynurenic acid (associated with neurotoxicity) via tryptophan
- Probiotics can block signal from gut pathogens
- Probiotics in animal models have shown an increase of tryptophan going to serotonin vs. kynurenic acid
    - Similar mechanism to anti-depressant medications

GUT – BRAIN AXIS CONNECTION



Kelly et al, 2015

DIET, INFLAMMATION AND MENTAL HEALTH



DIET, INFLAMMATION AND MENTAL HEALTH

> “A **dysfunctional intestinal barrier** could permit a microbiota driven **pro-inflammatory state** with implications for the brain. The sequence of this process is not yet clear. An **increase in gut permeability** could precede mucosal inflammation to induce the inflammatory response and thus culminate in a **feed-forward cycle between inflammatory responses and barrier dysfunction**. This could subsequently maintain and exacerbate the low-grade inflammatory response. Alternatively, **systemic inflammation could increase intestinal barrier permeability** and thus allow **translocation of commensal bacteria** with further implications for systemic inflammation.”
>
> **– KELLY ET AL., 2015**

AGENDA

01 INTRODUCTION

02 GUT-BRAIN AXIS

03 **GASTROINTESTINAL MICROBIOME AND MENTAL HEALTH**

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MICROBIOME AND DEPRESSION

Inflammation can induce symptoms of depression;
depression can induce symptoms of inflammation

- Those with clinical anorexia nervosa: intestinal microbiota has low diversity
- Correlation of fecal swabs (in humans) and depression diagnosis (55 patients)
- IBS and major depressive disorders: comorbidities
  - Chronic low-grade inflammation present in both

  (currently, the source of low-grade inflammation in those with depression is unclear)

Deans 2016; Dowlati et al., 2010; Folstein et al., 2007

MICROBIOME AND ANXIETY

Study on fermented milk (yogurt) and modulation of brain activity in women:

After ingestion, the women were less anxious, and showed this with brain imaging.

Study on a daily lactobacillus supplement vs. placebo (participants asked to respond to a negative stimulus):

People on probiotics had decreased rumination and decreased aggressive thoughts.

MICROBIOME AND ADHD

- 20-35% of children with Attention-Deficit Hyperactivity Disorder (ADHD) who are treated with medications do not respond to this therapy
  - What are we missing?

- Cesarean birth has been identified as a risk factor in ADHD development
  - Difference in exposure to microbes from mother

- Antibiotic use disrupts the gut microbiome and may allow pathogenic organisms to overgrow (not solely seen with ADHD)

- Treatment may include gluten-free diet, addition of micronutrients and/or probiotics/prebiotics

Esparham et al., 2014

MICROBIOME AND AUTISM

- Rodent model
  - Mice treated with bacteria had better communication than those who were not treated
  - Type of communication reduction considered “autistic-like behavior”

- Children diagnosed with ASD have dysbiosis (Kang et al) and a less-diverse microbiome

- ASD children:
  - Often have digestive symptoms and/or food sensitivities/allergies
  - Conflicting data on efficacy of gluten-free casein-free (GFCF) diet

Berding et al., 2016
Kang et al., 2013

MICROBIOME AND AUTISM

- Pediatric patients (n=30) with an ASD diagnosis on an exclusion diet (GFCF) or un-restricted diet with B-GOS prebiotic or a placebo (maltodextrin)
  - B-GOS is a galacto-oligosaccharide that feeds the bifidobacterium species

- Results:
  - Pediatric patients on a GFCF diet with this specific prebiotic showed a significant reduction in anti-sociability scores
  - The results showed that children on exclusion diets reported significantly lower scores of abdominal pain and bowel movement

Grimaldi et al, 2018

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HOW DO WE IMPROVE GUT-BRAIN AXIS FUNCTIONING?

- Reduce oxidative stress
  - Increase antioxidants via whole fruits/vegetables/grains/supplements

- Restore gut integrity and thereby restore gut function
  - Eat cultured foods
  - Use probiotics/prebiotics
  - Reduce overall emotional and “life” stressors
  - Consider zinc and butyrate (a SCFA) supplementation, which may help
  - Avoid vitamin A and D deficiency (both have associations with an increase in intestinal permeability)

Bischoff et al., 2014

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INFLUENCE OF DIET

The Standard American Diet (SAD) involves:

- High sugar intake = increased oxidative stress and immunosuppression

- High intake of saturated and trans fats versus unsaturated fats
  - Vitamin and mineral deficiencies
  - Insufficient fiber: regular fiber intake reduces adhesion of bacteria to intestinal wall, assists with mucosal repair
  - Insufficient phytonutrients: intake of phytonutrients (antioxidants) is anti-inflammatory

The above may increase oxidative stress, and may cause immune suppression, systemic inflammation and/or increased intestinal permeability.

CHANGING GUT MICROBIOME AND REDUCING INFLAMMATION

- Lower carbohydrate and higher fiber can positively change gut microbiome within days
- Increase fiber via fruits/vegetable sources, or supplements
- Increase fermented foods and probiotics
- Avoid alcohol
- Avoid stress/sleep deprivation
- Antibiotic use can reduce pathogenic bacteria

PROBIOTICS AND MICROBIOME

- No perfect “recipe” for altering microbiome: not a “one-size-fits-all” solution
- Recommendations need to be more individualized, especially with chronic health conditions

Rao et al, 2009; Tillisch et al, 2013

PREBIOTICS AND MICROBIOME

- Prebiotics are the food that our intestinal bacteria proliferate from

- Prebiotic inulin shown to alter the gut microbiome
  - 29 healthy adults given prebiotic inulin at 5 grams/day and 7.5 grams/day
  - After 21 days, had significantly altered microbiome composition
  - Increase in bifidobacterium and actinobacteria

CLINICAL PRACTICE APPLICATIONS

Reduce oxidative stress

- Life/environmental stress reduction
  - Meditation, yoga, exercise
  - Counseling, therapy

- Antioxidants
  - Vitamin C, vitamin E, zinc, glutathione
  - Phytonutrients from fruits, vegetables, seeds
  - Consider supplementation if unable to eat whole foods

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CONCLUSIONS

- ✓ Gut-brain axis is a bi-directional communication with multiple pathways.
- ✓ Gut health influences behavior and mental health outcomes in rodent research models.
- ✓ Probiotics alter gut microbiome in rodent and human models.
- ✓ Prebiotics alter gut microbiome in human models.
- ✓ Addressing inflammation via diet/nutritional changes can impact intestinal health (intestinal permeability) and behavior.

USEFUL REFERENCES FOR PROBIOTIC REVIEW

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Questions?

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