The role of the microbiome and the gut-brain axis in health and disease and potential therapeutic approaches

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LEARNING OBJECTIVES

1. Overview of the current research on the gut-brain axis with a focus on neurological conditions

2. Be aware of gut-brain interactions and their communication pathways

3. Understand how healthy gut function (Eubiosis) and unhealthy gut function (Dysbiosis) contribute to health and ill health

4. Be aware of evidence-based interventions to promote Eubiosis
The gut brain-axis is a biological pathway first detected in the 1960's when it came to light that the same neuropeptides were present in gut and brain (Pearse, 1969).

- It is a bi-directional signalling systems (endocrine, immune, autonomic, enteric and as well as the hypothalamic pituitary adrenal (HPA) axis) and microbiome metabolites and products.
- Comprises a physical route, via the vagal nerves, connecting brain-gut-brain.
- The enteric nervous system (ENS) is located in the gastrointestinal tract. It is a system of sensory neurons, motor neurons, and interneurons that extends throughout the tract and forms part of the ANS.
• The GBA implicated in many conditions, IBS, diabetes, obesity, developmental and psychological disorders, dementia and neurological conditions

• In recent years, the study of gut microbiota has become one of the most important areas in biomedical research

• So much so that the term is now microbiota-gut-brain axis (Rhee et al., 2009; Collins et al. 2012)
Gut filled with microbes, virus, fungi and archaea

- There are 14,000 viruses

- Each have unique MB but there are also signatures

- Microbes and their metabolites in constant communication with host cells and brain
The delicate equilibrium between eubiosis and dysbiosis in the bowels. Eubiosis is the condition in which saprophytic bacteria are present in the mucus-microbiotic layer of the bowel (either the small or the large one). Dysbiosis is a condition in which pathogenic bacteria (Pathogenic bacteria are represented with purple frame, non-pathogenic have a blue frame) predominate and cause changes in the intercellular tight junctions leading to tissue damage.

WHAT HAPPENS IN DYSBIOSIS?

- Low SCFA production
- Decreased/Unhealthy gut function
- Low microbial diversity
- Loss colonization resistance
- Gut inflammation (cytokines, endotoxins etc.)
- Insulin resistance
- Weak mucus layer
- Activation of antigens and exposure to bacterial toxin
- Increased lipid production

**Health effect**
- Diabetes
- Hypercholesterolemia
- Obesity
- Colorectal cancer
- Inflammatory bowel disease
- Diarrhea and constipation
- Metabolic syndrome
- Cardiovascular disease

- High SCFA production (synthesis of vitamins)
- Increased gut barrier function
- High diversity
- Colonization resistance (decreased risk of infections)
- Low gut inflammation
- Insulin sensitivity
- Healthy mucus layer
- Decreased cell proliferation
- Increased in anticancer potential
- Decreased metastasis
- Decreased angiogenesis
- Decreased toxicity
- Improved lipid metabolism
- Decreased oxidation stress
- Decrease bile content of bile acid
- Decrease blood cholesterol, glucose, and serum level of lipids
- Reduce body weight and visceral adipose tissues weight
Healthy CNS function

Healthy status
- Normal neuroendocrine, neuroimmune, neurotransmitter and endocrine function
- Healthy levels of immune cells
- Normal gut microbiota

Abnormal CNS function

Depression/ Stress
- Altered neuroendocrine, neuroimmune, neurotransmitter and endocrine dysfunction
- Increased pro-inflammatory biomarker
- Altered gut microbiota
- Increased gut permeability

Gut–Brain Axis

Healthy gut function

Abnormal gut function
Gut and Parkinson’s disease

More than 4 million papers on PD and gut dysfunction

Constipation may precede symptoms by at least a decade

James Parkinson recognized gut problems as core symptom of shaking palsy

Symptoms may vary across people and across lifespan

Our study: RCT feasibility study with probiotic and placebo groups

- 15 patients with PD assigned to probiotic or placebo group
- Fecal sample at baseline and 12 weeks
- Evidence of a PD signature approx. 100 species
- Dysbiotic microbiome but groups not different at baseline species prevalence
- Changes in prevalence and abundance of beneficial microbes between the two groups at 12 weeks

Placebo data Time 1 and 2 - 100% presence across patients through to 58%
CONTROL GROUP DIMINISHED PREVALENCE OF GOOD BACTERIA AFTER 12 WEEKS

<table>
<thead>
<tr>
<th>Species</th>
<th>Function</th>
<th>Probiotic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecalibacterium</td>
<td>Most abundant and important commensal bacteria of the human gut microbiota</td>
<td>✓</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>Oxalate &amp; Butyrate</td>
<td>✓</td>
</tr>
<tr>
<td>Lachnoclostridium</td>
<td>Reduced in bowel cancer</td>
<td>✓</td>
</tr>
<tr>
<td>Butyricoccus</td>
<td>Butyrate producer natural probiotic</td>
<td>✓</td>
</tr>
<tr>
<td>Christensenellaceae R-7 group</td>
<td>Associated with low BMI</td>
<td></td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Hydrocarbon muncher</td>
<td>✓</td>
</tr>
<tr>
<td>NK4A214 group</td>
<td>Prevent Type 2 diabetes</td>
<td>✓</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>Hydrocarbon muncher</td>
<td></td>
</tr>
<tr>
<td>Prevotella</td>
<td>Anti-inflammatory properties</td>
<td></td>
</tr>
<tr>
<td>Roseburia</td>
<td>prevents intestinal inflammation</td>
<td></td>
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</tbody>
</table>
### Other Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Presenting gut symptoms</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>Altered Microbiome compared to controls</td>
<td>Levi et al., 2021</td>
</tr>
<tr>
<td>Dementia</td>
<td>Gut barrier dysfunction</td>
<td>Stadlbauer et al., 2020</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>Altered Microbiome compared to controls</td>
<td>Li et al., 2019</td>
</tr>
<tr>
<td>Obesity</td>
<td>Altered Microbiome compared to controls</td>
<td>Companys et al., 2021</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Altered Microbiome compared to controls</td>
<td>Zhu et al., 2021</td>
</tr>
<tr>
<td>Neurodevelopment disorders</td>
<td>Altered Microbiome compared to controls</td>
<td>Bojovic´ et al., 2020</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>Altered Microbiome</td>
<td>Coker et al., 2020</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>Altered Microbiome</td>
<td>Hassain et al, 2020</td>
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</tbody>
</table>
DIET AND THE MICROBIOME

- Know far less than we ought to about diet and MB
- Temporary change seems to have only temporary effects\(^1\)
- Still do not know what constitutes gastrointestinal gravity and holds the MB in stasis – eubiotic or dysbiotic

\(^{1}\) Leeming et al., 2019, Nutrients 10.3390/nu11122862
WHAT DO WE KNOW ABOUT DIETARY INTERVENTIONS?

• Permanent rather than transient changes to the core gut microbiota required for long-term impact on health outcomes

• Diet–microbe interventions must consider the capabilities of an individual to make sustainable dietary changes because change occurs 24-48 hours after dietary intervention but then MB reverts ¹

• Many factors affect efficacy of dietary interventions including diurnal fluctuations and individual variability

OTHER FACTORS

1 Kaczmarek and colleagues notes several species related to eating time.

2 Collado et al., found that timing of meal affects salivary microbial profile in pro-inflammatory way, affecting body weight, cortisol rhythm, basal metabolic rate, glucose tolerance and body temperature.

Effect of fasting or time-restricted feeding on the gut microbiota are still unknown.


HEALTHY FOOD: FIBRE

One study found fibre intake positively correlated with a change in abundance of 15% of the microbial community the following day.¹

A 2018 systematic review and meta-analysis observed the effect of fibre on the gut microbiota from 64 studies. Dietary fibre interventions, particularly fructans and galactooligosaccharides (GOS), were found to increase faecal abundance of Bifidobacterium and Lactobacillus species but did not affect alpha-diversity.²

Johnson et al found that microbial composition related to food choices rather than the conventional nutrient profile typically used in nutrition research,


Only short-term effects documented as with diet: because a healthy gut may have no biological niche for species engraftment

Not known whether there can be LT effects in dysbiotic gut

While probiotics may be transient, they have the capacity to alter the composition of the gut microbiota, in turn influencing the production of beneficial fermentation-derived metabolites

In addition, clinical effects have been shown without evidence of colonisation in probiotic studies ¹

DYSBIOTIC GUT

Presents special case

Must be improved to create a biological niche and encourage engraftment of new species (beneficial)
THREE-PRONGED APPROACH

Prebiotics
- Apple
- Artichoke
- Banana
- Onion
- Tomato

Probiotics
- Yogurt
- Miso
- Kimchi
- Pickles
- Tempeh

Diet
OTHER FACTORS

Sunshine
Fresh air
Diurnal fluctuations
Sleep
Eating times and patterns
Exercise
Long term sustainable change
SUMMARY

1. Gut brain axis potential role in many conditions

2. Eubiosis and dysbiosis important clinical markers

3. Evidence based treatment includes prebiotic, probiotics, high fibre diet, exercise, limiting toxins and antibiotics
LEARNING OUTCOMES

Consider gut symptoms and dysbiosis in the context of current research.

Consider gut dysbiosis alongside non-gut based symptoms in presenting patients.

Consider recommending dietary change and supplementation for gut dysbiosis.

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REFERENCES


