Gut Feelings: How the microbiome influences behavior

Jane A. Foster, PhD
The Speaker
Gut-Brain Axis

Brain

Microbiota

- Immune System
- Metabolism
- Gut hormones/Neuroendocrine system
- ANS/ENS
THE BRAIN MODULATES GUT FUNCTION

1833 - Beaumont
THE BRAIN MODULATES GUT FUNCTION

- Association of emotional state and GI function in patients with functional bowel disorders
- In healthy volunteers, alterations in gut function are associated with experimental stressors
- Affective state alters pain perception in IBS patients
- Strong association of generalized anxiety disorder and IBS
- CNS acting drugs often prescribed and evidence of effective for treatment of GI patients

Aziz and Thompson, 1998
Mental Health May Depend on Creatures in the Gut

The microbiome may yield a new class of psychobiotics for the treatment of anxiety, depression and other mood disorders
What do we know about microbiota?

- The GI tract of an adult human contains 100 trillion viable bacteria
- More than 1000 species represented in healthy individuals:
  - high interpersonal variability in bacterial composition
  - gut microbiota profile show minimal intrapersonal variability over time
- Host and microbiota have a symbiotic relationship
- Microbiota are essential to host pathogen defense, nutrient uptake and metabolism, and are central to brain development
- An individual’s profile of microbiota is influenced by genetics, age, sex, and diet
• Exposure to microbes and colonization occurs starting at birth and continues through development.

• In healthy infants, dynamic changes in microbiota composition and diversity over the first year of life - influenced by diet (breast vs bottle-fed) and mode of delivery (vaginal vs c-section).
Foster Lab Research

- We use animal models to understand how brain-body communication influences brain development and behaviour

- We are interested in understanding how changes in brain-body communication contribute to mental illness
Do microbiota influence brain function and behaviour?
The germ-free (GF) mouse

- Model was established in 1957

- GF mice are raised in a sterile/gnotobiotic environment and therefore have no commensal bacteria
The starting point...

**Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice**

Nobuyuki Sudo¹,², Yoichi Chida¹, Yuji Aiba³,⁴, Junko Sonoda¹, Naomi Oyama¹, Xiao-Nian Yu¹, Chiharu Kubo¹ and Yasuhiro Koga³

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GF mice spent more time in the open arms of the EPM

GF mice showed increased open arm entries
Several CNS genes altered in GF mice are known to influence anxiety-like behaviour

- Brain derived neurotrophic factor
- Serotonin receptors
- Serotonin transporter
- NMDA receptors
- Glucocorticoid receptors

DIFFERENCES INFLUENCED BY STRAIN AND SEX
Lessons from germ-free mice

- microbiota influence anxiety-like behaviour
- microbiota influence the development of stress circuits and stress-reactivity
- Question is:

**Whether or not the microbiota itself are mediating the effects observed in GF mice?**
The host microbiota contributes to anxiety-like phenotype

Bercik et al. 2011

A

B

C

Relative intensity

Relative front

NIH Swiss mice

P < 0.01

P < 0.01

Latency to step-down (sec)

SPF  GF+  GF+

NIH Swiss microbiota

Latency to step-down (sec)

SPF  GF+  GF+

BALB/c mice

P < 0.05

P < 0.01

BALB/c microbiota

Bercik et al. 2011
16s rRNA analysis of bacterial composition

Alpha Diversity Reduced in Balb/C mice

Two clusters using Bray-Curtis Distance
Lessons from host genetics

• Using different strains of mice we show that:

  ★ Balb/C and CD1 mice show differences in microbiota composition and diversity

  ★ Differences in anxiety-like behaviour and activity can be linked to microbiota composition at the phyla level

  ★ HPA axis activation to immune challenge is associated with microbiota composition at the phyla level

• Additional ongoing analysis will determine whether species differences in microbiota can be linked with behaviour, stress reactivity, and brain structure
Microbiota in humans and mice

- At the species level, microbiota in mice are unique when compared to human microbiota.
- At the division level, there is considerable similarity between mice and human microbiota.
- Two bacterial division, the Bacteriodetes and the Firmicutes dominate in both mice and human microbiota.

Ley et al. 2005, PNAS, 102:11070-75
45% contribution of host genetics to composition of the microbiome
How do microbiota communicate with the brain?

1. Neural
2. Humoral
3. Cellular
4. Metabolites
5. Neuroactive molecules
Neurochemicals are present in bacteria

• Has been known for decades - what’s new is the consideration of their role outside the gut interior milieu

• Partial list of neurochemicals
  - GABA – Bacillus, Lactobacillus, Clinical bacterial pathogens
  - Somatostatin - Bacillus subtilis
  - Dopamine – Escherichia, Bacillus, Lactococcus, Lactobacillus, Strep.
  - Serotonin – Streptococcus, Enterococcus, Escherichia, Lactobacillus
  - Acetylcholine – Lactobacillus, Bacillus
  - Short chain fatty acids – fermentation, numerous strains

• Specific receptors have been demonstrated - 100% homology of E. coli EnvY gene for high affinity opioid binding site
Psychobiotics: How gut bacteria mess with your mind

Gut bugs can change the way our brains work, offering new ways to relieve problems like stress, anxiety and depression, say two leading professors.

News Feature: Microbes on the mind

Could the gut microbiome have a critical role in brain and behavior? The notion is starting to gain acceptance amongst both researchers and funders.

Helen H. Shen
Science Writer
5 Vital Probiotics That Boost Your Brainpower

- Elie Metchnikoff, Russian scientist, Nobel Prize in 1908
- Inspired Minoru Shirota to investigate the connection between bacteria and good GI health
- Shirota is the inventor of Yakult - the yogurt-like probiotic drink containing Lactobacillus casei strain Shirota - 1930
Probiotics influence anxiety-like and depressive-like behaviour in mice

Bravo et al 2011
Evidence of a link between microbiota and anxiety and depression is slowly emerging

British Journal of Nutrition

Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects

- Lactobacillus helveticus (R0052) and Bifidobacterium longum (R0175) or placebo administered to healthy volunteers for 30 days
- Reduced self-report psychological stress levels

Messoudi et al 2011
Evidence of a link between microbiota and anxiety and depression is slowly emerging

- Commercially available Fermented Milk Product with Probiotics (*Bifidobacterium anaimalis*, *Lactococcus lactis*, *L. delbrueckii*, *Streptococcus thermophilus*)

- 28 days administration to healthy women

- reduced activity in widely distributed brain network 4 week post treatment to negative emotion recognition task

_Tillisch et al 2013_
Evidence of a link between microbiota and anxiety and depression is slowly emerging

A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood

Laura Steenbergen\textsuperscript{a,b,*}, Roberta Sellaro\textsuperscript{a,b}, Saskia van Hemert\textsuperscript{c}, Jos A. Bosch\textsuperscript{d}, Lorenza S. Colzato\textsuperscript{a,b}

Brain, Behavior, and Immunity

- 28 days administration of “Ecologic Barrier” containing \textit{B. bifidum W23, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24,} and \textit{L. lactis (W19&W58)} compared to placebo to healthy individuals

- Probiotic groups showed reduction in cognitive reactivity to sad mood, specifically aggressive and ruminative thoughts
What are the good bacteria?

- Bifidobacteria (Actinobacteria)
- Lactobacillus (Firmicutes)
Microbiota and Major Depression

Correlation between the human fecal microbiota and depression


Altered fecal microbiota composition in patients with major depressive disorder

Haiyin Jianga,1, Zongxin Linga,1, Yonghua Zhanga,1, Hongjin Macci, Zhanping Mad, Yan Yin c, Weihong Wang e, Wenxin Tang c, Zhonglin Tan c, Jianfei Shi c, Lanjuan Li a,2, Bing Ruan a,*

in press
Does the gut–brain axis play a role in childhood neurodevelopmental disorders, such as autism?

- GI disturbances are prevalent in children with autism (Buie et al., 2010)
- The number of GI symptoms is shown to be associated with the severity of autism (Adams et al., 2011)
- Several studies have now reported changes in microbiota profile in patients with autism (Finegold et al., 2002, Song et al., 2004, Parracho et al., 2005, Finegold et al., 2010, Adams et al., 2011, Williams et al., 2011, Williams et al., 2012)
- Studies considering possible mechanisms for gut-brain communication in autism suggest that an altered metabolic phenotype in association with microbiota dysbiosis may contribute to ASD (MacFabe et al., 2007, Williams et al., 2011).
- Short term treatment with antibiotics has been reported to improve in behavioural symptoms in some patients with autism (Sandler et al., 2000)
Probiotics and Autism

Exposure to viral or bacterial infection in utero leads to autistic-like behaviour in offspring

Hsiao et al. 2013 - Cell 155:1451-1463
Probiotics and Autism

Hsiao et al 2013 - Cell 155:1451-1463
Probiotics - Hype or Hope

Nutrition Reviews Advance Access published September 13, 2015

Special Article

Systematic review of evidence to support the theory of psychobiotics

Amy R. Romijn and Julia J. Rucklidge

stay tuned...
Other approaches…

Fecal Microbiota Transplantation — An Old Therapy Comes of Age
Ciarán P. Kelly, M.D.
Other approaches…
Other approaches…
“It’s not stress that kills us, its our reaction to it”

–Hans Seyle

“Your state of mind is dependent on your state of gut”

–John Cryan
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