Advances in Understanding and Treatment of Irritable Bowel Syndrome

Prof. Ted Dinan MD, PhD
Department of Psychiatry and Alimentary Pharmabiotic Centre, University College Cork
Irritable Bowel Syndrome (IBS)

- IBS affects approximately 10-20% of the general population.
- It is the most common disease diagnosed by gastroenterologists.
- It is characterized by a group of symptoms in which abdominal pain or discomfort is associated with a change in bowel pattern.
- Current therapies are frequently ineffective.
Patient Characteristics

- 70% diarrhoea predominant
- 20% alternating
- 10% constipation predominant

Psychiatric illness in the form of depression, anxiety or somatization disorder is present in about 30% of cases
Psychological factors

- Stressful life events
- Sexual and physical abuse
- Psychiatric illness
- High trait anxiety
- Increased health care seeking
- Poor health-related quality of life
Visceral hypersensitivity

- 70% of IBS patients have pain at lower volume and pressures when a balloon is inflated in the bowel
- Diarrhoea-predominant patients have the lowest thresholds
- Spinal hyperexcitability with activation of NO and other transmitters is thought to be the mechanism
Stress Alters Brain-Gut Axis

Diagram showing the interaction between stress, the hypothalamus, the pituitary gland, the adrenal cortex, the immune system, and the gastrointestinal (GI) tract. Key components include CRF, ACTH, cortisol, and neurotransmitters. The diagram illustrates how stress can alter brain-gut axis function, impacting neurotransmitter levels, adrenal gland activity, immune cell activity, and GI motility and epithelial barrier integrity.
IBS response to CRH Infusion

ACTH (ng/l)

Healthy subjects
IBS

Time (min)

Healthy controls
IBS

cortisol (nmol/l)

Healthy controls
IBS
Are plasma cytokine levels altered in IBS?
Cytokine Balance

Pro-Inflammatory
- TNFα
- IFNγ
- IL-8
- IL-12

Anti-Inflammatory
- TGFβ
- IL-10
- IFN α
- IL-11
Cytokines in IBS

Plasma Levels of IL-6 in IBS patients and Healthy Controls

Plasma Levels of sIL-6R in IBS patients and Healthy Controls

Plasma Levels of IL-4 in IBS patients and Healthy Controls

Plasma Levels of TNF in IBS patients and Healthy Controls

Dinan et al, Gastroenterology, 2006
Plasma Cytokine Profiles in Females With Irritable Bowel Syndrome and Extra-Intestinal Co-Morbidity

Paul Scully, PhD\textsuperscript{1}, Declan P. McKernan, PhD\textsuperscript{1}, John Keohane, MB, MRCP\textsuperscript{1}, David Groeger, PhD\textsuperscript{1}, Fergus Shanahan, MD, FRCP, FRCP\textsuperscript{1}, FACP, FCCP\textsuperscript{1}, Timothy G. Dinan, MD, PhD, DSc, FRCPsych\textsuperscript{1} and Eamonn M.M. Quigley, MD, FRCP, FACP, FACG, FRCP\textsuperscript{1}

\* $p<0.05$; IBS & Comorbid Patients ($n=120$) compared to Healthy Volunteers ($n=53$)
Biomarkers in IBS

- Elevated plasma IL6
- Altered tryptophan metabolism
- Enhanced CRH response

$\Delta$ACTH and IL-6 correlation $r=0.61$, $df=40$, $p<0.05$

Dinan et al Gastroenterology 2006;130:304
Toll-Like Receptors - A role in stress regulation of brain-gut axis
Whole Blood from IBS Patients Stimulated with TLR Agonists

(a) IL-1β (pg/ml)

(b) IL-6 (pg/ml)

(c) IL-8 (pg/ml)

(d) TNF-α (pg/ml)

UT Pam3Csk HKLM Poly I:C LPS Flagellin FSL1 Imiquimod ssRNA40

 Ctrl IBS

*significant, **very significant, ***very very significant
The Normal flora

400-500 species including:
- Bacteroides
- Eubacterium
- Peptostreptococcus
- Bifidobacterium
- Ruminococcus
- Bacillus
- Fusobacterium
- Clostridium
- Lactobacillus
- Enterococcus
- Enterobacter
- Anaerobes

>> Aerobes

Jejunum: $10^{3-4}$
Terminal Ileum: $10^{7-9}$
Colon: $10^{10-12}$

Many bacteria remain unculturable!!
Probiotics

First described by Metchnikoff in 1908

“Live microbial food ingredients that alter the microflora and confer health benefit”

Many claims; less evidence; little science!
Prebiotics

“Non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon”

Duggan et al, 2002.

- Oligosaccharides in human breast milk
- Inulin
- Fructose oligosaccharides
  - Promote growth of *bifidobacteria* and *lactobacilli*

Prebiotic + Probiotic = Synbiotic
Mode of Action of Probiotics?

- Competition with, and exclusion, of pathogens
- Anti-bacterial:
  - Produce bacteriocins
- Enhance barrier function, motility
- Produce valuable metabolites
- Enhance host immunity
  - Cytokine modulation
Study Design

Weekly assessments of symptoms
Stool analysis at 0, 8 and 12 weeks
N=25 per group

O’Mahony et al, Gastroenterol, 2005
Probiotic Strains

- *Bifidobacterium*
- *Lactobacillus salivarius*

- selected on the basis of results from *in vitro* and *in vivo* studies, ELISA and gene array analyses which identified properties/characteristics considered beneficial in IBS

- $10^{10}$ bacteria/ml in 100 ml of milk
Composite Score

Week

- Placebo
- Lacto
- Bifido
O’Mahony et al,
Gastroenterology, 2005

* p = .001
**Global Assessment of Symptom Relief**

- B. infantis $1 \times 10^8$
- B. infantis $1 \times 10^6$
- Placebo

P-value = 0.0118

Whorwell et al, AJG 2006
How might probiotics influence mental processes?
Hippocampus
Amygdala

Nissl-stained section

Acetylcholinesterase-stained section
Lactobacillus strain, GABA receptor expression and behaviour

Effects of Vagotomy

A

Open field

<table>
<thead>
<tr>
<th>% Time in centre</th>
<th>Entries to centre</th>
<th>Motor activity</th>
<th>Forced swim test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham/Broth</td>
<td>sham/L.rhamnosus (JB-1)</td>
<td>Vx/Broth</td>
<td>Vx/L.rhamnosus (JB-1)</td>
</tr>
</tbody>
</table>

B

DG | CA3 | CA1

C

DG | CA3 | CA1

Sham/Broth

Sham/L. rhamnosus (JB-1)

Vx/Broth

Vx/L. rhamnosus (JB-1)
Microbiota Immune Endocrine Interactions

Stress

- Altered 5HT
- ↓ tryptophan
- ↑ IDO
- ↑ IFNγ/IL-6
- GR resistance
- ↑ Cortisol
- ↑ CRF/AVP

Probiotics
- ↓ Pro-inflammatory cytokines