LPS binding protein (LBP) as marker of intestinal permeability to predict the effect of treatment with probiotics?

BCM Haarman, S El Aidy, S van Hemert, J Fu, EAM Festen, IEC Sommer

University of Groningen, University Medical Center Groningen, Department of Psychiatry, Groningen, The Netherlands

b.c.m.haarman@rug.nl

Background

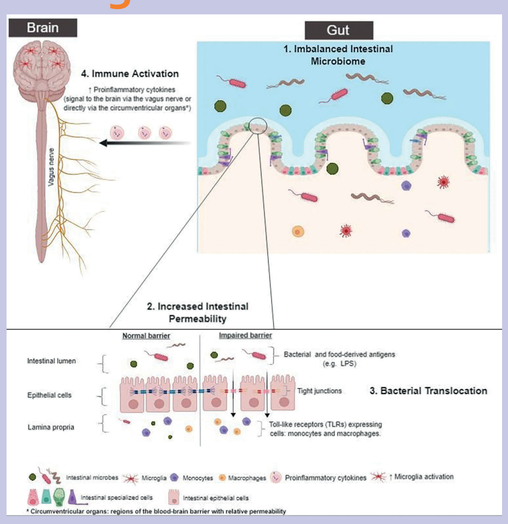

Figure 1 Overview of the of the gut derived immune activation leading to neuronal inflammation in SCZ and BD patients.

- In bipolar disorder (BD) and schizophrenia (SCZ) recent investigations have pointed to the gut-brain axis as a new venue for treatment[1-3], with increased inflammation stemming from increased intestinal permeability[2] to further affect brain functioning in a significant subset of patients (figure 1)[3].
- In multiple studies increased intestinal permeability in SCZ and BD is demonstrated by translocation of food and bacterial antigens, as well as intestinal microbiome disturbances[2-3].
- This is associated with dysregulation of the immune system, precipitation and exacerbation of psychiatric symptomatology, metabolic complications and increased cognitive impairment[3].
- Probiotics are promising candidates to improve patients' symptomatology and functioning and there are rational methods to personalize its application with biomarkers that measure intestinal permeability and subsequent immune activation[1-3].
- Lipopolysaccharide binding protein (LBP) is a soluble acute-phase protein that bind to bacterial lipopolysaccharide (LPS) to elicit immune responses by presenting the LPS to important cell surface pattern recognition receptors[3].
- Therefore LBP is considered to be a marker for intestinal permeability driven by microbial translocation[3].
- In a small pilot study we investigated how the LBP concentration in SCZ compared to healthy controls.

Pilot study

Methods

- In this post-hoc analysis of a study investigating simvastatin augmentation for recent-onset psychotic disorder (SMRI 12T-008)[4], twenty-four patients with recent onset schizophrenia and twenty-four healthy controls were included in the analyses.
- All subjects underwent psychiatric interviews and a blood draw for the measurement of LBP.
- LBP was measured in 1000-fold diluted blood samples in triplicate, according to the instructions of the manufacturer, using a commercially available ELISA kit (Human LBP ELISA kit, Hycult Biotech, the Netherlands).
- We compared the LBP between the patients and control groups with Student's *t*-test.

Results

- There was no difference in gender between the groups.
- We found a mean level of LBP of 9.3ng/ml (SD 5.5) in the controls, which was significantly lower than the 13.4ng/ml (SD 7.6) found in the SCZ patients (p=0.05).

Discussion

- Although the pattern of LBP levels might be complex in this patient population, it is rational to hypothesize that probiotic treatment may be more effective in patients with higher serum LBP, corresponding to increased intestinal permeability[5].

Probiotic formulation for patients with psychotic or bipolar disorder with increased intestinal permeability (GUTS)

Objectives

- In a novel randomized controlled trial we will investigate
  - Whether intestinal permeability improving probiotics have an effect on symptom severity in patients with psychotic or bipolar disorders that have increased intestinal permeability (LBP ≥ median)
  - Which factors (LBP, intestinal inflammation (fecal calprotectin), intestinal microbiome, and others) can best predict individual treatment response to probiotics
- We will also investigate whether treatment with probiotics have a beneficial effect on immune parameters, metabolic syndrome features, cognition, side-effects, general functioning and gastrointestinal complaints

Methods

- 145 patients, aged between 18-65 years, diagnosed with a psychotic or bipolar disorder with a Brief Psychiatric Rating Scale (BPRS) score >41 and a LBP ≥ median will be randomized to treatment twice daily with either a probiotic formulation or placebo in addition to their regular treatment (figure 2).
- The probiotic formulation (Ecologic Barrier (Winclove, Amsterdam); 2g 2dd; Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19, Lactococcus lactis W58; $1x10^{10}$ colony forming units/day) is specifically selected for its beneficial effect on intestinal permeability[5-7].
- Outcome measurements include BPRS (primary), immune parameters, metabolic syndrome features, cognition (Brief Assessment of Cognition in Schizophrenia (BACS), side-effects, general functioning (World Health Organization's Disability Schedule (WHO-DAS II) and gastro-intestinal complaints).
- Stool and blood samples will be analyzed to identify optimal biomarkers (serum LBP, fecal calprotectin, intestinal microbiome) for response to probiotics.

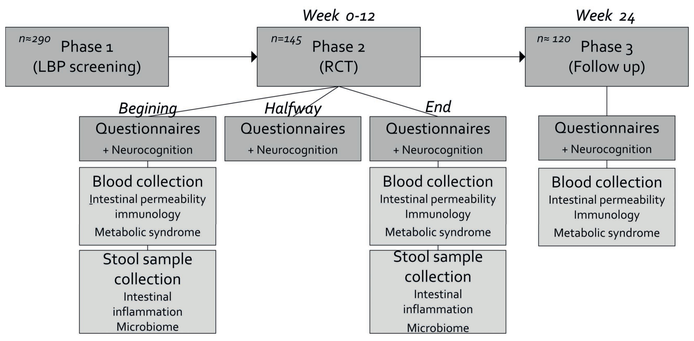

Figure 2 Schematic overview of the GUTS probiotic RCT study phases and measurements

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