FENS 2015 Berlin
Session : Nutrition and health throughout life cycle The role of grain products
Cereal fibre and whole grain : impact on gut microbiota and health

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Conflict of interest regarding this presentation:

I have no conflict of interest to report in relation to this presentation.
The Gut Microbiota: an internal organ we feed everyday for the maintenance and/or recovery of health

1. Human cells: 30000 genes (genome)
2. Bacterial cells: 1600 genes (microbiome)
3. The gut microbiota contains up to 1000 species \(10^{14}\) cells dominated by 3 (of 70) divisions:
   - Firmicutes (E. rectale–Cl. Coccoides, Cl. leptum)
   - Bacteroidetes (Bacteroides, Prevotella)
   - Actinobacteria (Bifidobacterium)
4. Bacteria are classified as gram negative (LPS) or gram positive

The Gut Microbiota: an internal organ we feed everyday for the maintenance and/or recovery of health

10\(^{14}\) bacterial cells in the gut

100 fold more gene in the microbiome than in the human genome

Production of hundreds of metabolites, mostly from nutrients escaping the digestion in the upper part of the gut

A fragile equilibrium.....
Complex carbohydrates, fermentable dietary fibers

Saccharolytic bacteria

Goblet cell Mucus production

Akkermansia

Gut Barrier Endotoxemia

Intestinal transit

Gut microbial activity

Host metabolism

GLP-2

GLP-1

Insulin secretion/response

GPR41

GPR43/41

TGR5

TGR5

H₂S

Sulfide

Propionate

Acetate

Butyrate

Tyrosine

Phenol

Sulfide

Goblet cell Mucus production

L cell

GLP-2

PYY

Intestinal transit

appetite

Insulin secretion/response

Delzenne et al modified from Diabetologia, 2015
Dysbiosis: disturbances of gut microbiota composition and function
Dysbiosis (changes in composition and/or function of the gut microbiota) is associated with diseases characterized by disturbances of immunity (inflammation) and energy metabolism.

Changes at the phyla diversity, species/genders, and gene functions

Delzenne et al, Diabetologia 2015

Undernutrition, severe infections, renal diseases, cancer

Sheridan et al, Gut microbes 2014

- Nearly **25** publications describing the changes in bacterial populations in (obese) diabetic versus healthy human subjects.

- Characteristics of the dysbiosis
  - Decrease in bacterial diversity
  - Changes in bacterial functions (drug and oxidative stress resistance)
  - Increase in potentially harmful bacteria (i.e. Desulfovibrio spp., Proteobacteria, Bacteroides-Prevotella)
  - Decrease in beneficial bacteria (Bifidobacteria, *F. Prausnitzii* (anti-inflammatory), Roseburia intestinalis (butyrate producer), Akkermansia muciniphila (gut barrier))
Dysbiosis compromises the gut barrier function and allows the translocation of bacterial elements like lipopolysaccharides (LPS) which alters host metabolism.

Serum LPS increases in diabetic patients.

Modified from P. Cani.
The administration of Lactobacillus acidophilus NCDC13 is associated with an increase of Bifidobacterium spp. (Eubiosis).

Probiotic approach: administration of selected live bacteria

Prebiotic approach: feed the existing ecosystem

Dysbiosis
Feeding the gut microbiota with non digestible carbohydrates may modulate the gut microbiota. 

Fermentation of Non digestible Oligo- or polysaccharides
Fructans (inulin), arabinoxylans
Glucans, resistant starch

Prebiotic effect?
Development of «beneficial bacteria»
Bifidobacteria, Akkermansia
Gas and metabolites (SCFA)

Health effect

Question: do whole grain and related fractions have prebiotic properties?
Whole grain exert prebiotic effects in animal studies

• Whole grain oat (vs low bran oat) in mice: improves insulin sensitivity, total cholesterol. These changes are related to modifications of the gut microbiota (increase in *Prevotellaceae*, *Lactobacillaceae*, lower *Clostridiaceae*…) (Zhou et al J Nutr 2015)

• Whole grain barley reduces plasma LPS-binding protein and MCP-1. It increases caecal short chain fatty acids, decreases *Bacteroides fragilis*, increases *Akkermansia muciniphila*, and increases *Bifidobacteria* -only in high fat diet-fed rats (Zhong et al Br J nutr 2015).

• Effect of processing? Whole grain barley to barley malt given in rats for 4 wks have differential effect on the gut microbiota (Zhong et al Mol Nutr Food Res 2015)
Whole grain consumption in humans modulates the gut microbiota and improves glycemia and inflammation: proposal of the mechanisms

60g – 4 weeks in normal weight and overweight subjects

Martinez et al, ISME J 2013; Walter et al Gut microbes 2013
Whole grain, fractions and composition in terms of « prebiotic candidates »

Table 1. Definition and distribution of NDC in wheat (% dry matter)

<table>
<thead>
<tr>
<th>botanical components</th>
<th>whole grain</th>
<th>bran flour</th>
<th>aleurone cells and germ</th>
<th>starchy endosperm</th>
</tr>
</thead>
<tbody>
<tr>
<td>milling fractions</td>
<td>whole meal</td>
<td>bran flour</td>
<td>aleurone flour</td>
<td>white flour</td>
</tr>
</tbody>
</table>

- **Arabinoxylan [2,**19]**
  - Carbohydrates consisting of $\beta$ (1,4)-linked D-xylopyranosyl residues to which a-L-arabinofuranose units are linked as side chains. Some arabinoses can be substituted with ferulic acid. The degree of substitution refers to the arabinose moieties on the xylose backbone and is further described as $A/X$ ratio.
  - 4-9 % 12.7-22.1 % 60-70 % 1.4-2.8 %

- **Fructan [20-22]**
  - Carbohydrates of fructosyl units with or without one glucosyl unit. Wheat fructans contain both $\beta$ (1,2) and $\beta$ (6,2) linkages and have an avDP of up to 19 with a similar molecular weight distribution in the different fractions. Some fructo-oligosaccharides with an estimated DP of 5-7 in most whole grain whereas fructans in wheat flour have been reported to have a highest DP of 7-8 and ≥16.
  - 0.6-2.6 % 2.7-3.7 % 1.9 % 1.5-1.6 %

- **$\beta$-glucan [2,22,23]**
  - Carbohydrates consisting of a linear homopolymer arranged in blocks of consecutive $\beta$ (1,4)-linked d-glucose residues separated by single $\beta$ (1,3)-linkages. The chain mainly consists of cellobiosyl (58-72%) and cellohexaose (20-34%) units; some cellulosic blocks having more than four residues.
  - 0.5-1.4 % 1.4-1.8 % 0.9 % 0.3-0.4 %

- **Resistant starch [24]**
  - The starch consists of 2 main structural components, the amylose, which is essentially a linear polymer in which glucose residues are $\alpha$-D-(1,4) linked, and amylopectin, which is a larger branched molecule with $\alpha$-D-(1,4) and $\alpha$-D-(1,6) linkages. Resistant starch is defined as that fraction of dietary starch, which escapes digestion in the small intestine; it is measured chemically as the difference between total starch obtained from homogenized and chemically treated sample and the digestible starch generated from non-homogenized food samples by enzyme digestion. It is subdivided into 4 fractions: RS1, RS2, RS3, and RS4.
  - 16.4 % 1.1 % 0.8 % (in germ)

- **Cellulose [2,22]**
  - Cellulose is a homopolymer of glucose linked by $\beta$-(1,4) linkages only.
  - <5 % 8-10 % 3.9 % 0.5-0.6 %

- **Galacto-oligosaccharides [20,25]**
  - Galacto-oligosaccharides called also $\alpha$-galactosides or raffinose family oligosaccharides (RFOs) are soluble low-molecular weight oligosaccharides, such as raffinose (trisaccharide), stachyose (a tetrasaccharide), verbascose (a pentaosaccharide) and other oligosaccharides formed by $\alpha$-(1,6)-galactosides linked to C-6 of the glucose moiety of sucrose.
  - Identified not determined Identified (Raffinose: 7.2 % in germ) not determined

do you need this slide now you have inserted the new diagram? I don't think it can be read.

Answer: Yes, because I would like to show that it is not the same compound which is present in majority in the same fraction, and therefore, we could explain some differences between fractions by referring to major fermentable fiber present in it.

I think that it would be interesting for some readers to have a view of this table and of the reference because there are really not a lot of such descriptions in the literature (useful for structure activity relationship)

SIWS; 15/10/2015
Questions

• Could resistant starch be implicated in gut microbiota modulation and host health?

• Wheat bran: are all effects on host metabolism related to the gut microbiota?

• Is there an interest in aleurone fraction versus wheat bran?

• Can arabinoxylans (mostly present in aleurone fractions) be considered as prebiotics?
Resistant starches are drivers of gut microbial changes related to improvement of host health

- Several types of RS (few data on RS 1, related to whole grain structure)
- RS modulate the gut microbiota differently in mice and man (interpretation)
- Some Bacteria may be crucial (*Ruminococcus bromii*) for starch degradation
- Increase in *Faecalibacterium prausnitzii* and *Eubacterium rectale* by RS could be interesting (butyrate producer, anti-inflammatory properties)

*Bindels et al Current opinion in Clin Nutr and Metab 2015*
Questions

• Could **resistant starch** be implicated in gut microbiota modulation and host health?

  **Wheat bran**: are all effects on host metabolism related to the gut microbiota?

• Is there an interest in **aleurone fraction** versus wheat bran?

• Can **arabinoxylans** (mostly present in aleurone fractions) be considered as prebiotics?
Protocol to evaluate the effect of wheat bran fractions on obesity

- Data related to the Branding project (Flanders, Belgium)
- Comparison of wheat bran fractions differing by the particle size, but with similar nutrients composition
- When given in high fat diet fed mice, both wheat bran fractions (small and large particle size) do not modulate the gut microbiota composition in a similar way, and also have different effects on body weight and fat mass
- Only Bran with large particle size have lipid binding effect and increase fat fecal excretion, an effect contributing to a decrease in adiposity (independent on the gut microbiota)

*Unpublished data, Suriano F et al BRANDING project*
Questions

• Could resistant starch be implicated in gut microbiota modulation and host health?

• Wheat bran: are all effects on host metabolism related to the gut microbiota?

Is there an interest in aleurone fraction versus wheat bran?

• Can arabinoxylans (mostly present in aleurone fractions) be considered as prebiotics?
Aleurone (bran fraction) has greater effect on gut bacteria than crude fibre

(10% in high fat diet fed mice for 8 wks)

Arabinoxylans improve host metabolism by changing gene expression, those effects being correlated to the changes in gut microbiota.

Mice treated for 4 wks with 10% wheat arabinoxylans in high fat diet.
Interest of cereal products as prebiotic fibers

Relevance in diabetic/overweight humans? AX decrease glycemia in most studies, rare papers reporting gut microbiota analysis (review Delzenne et al. Diabetologia 2015)
Conclusions

- Whole bran and most of its fractions have prebiotic properties (related to obesity).
- Many fractions increase the activity of «interesting bacteria» ($Roseburia$, $Bifidobacteria$, $Akkermansia muciniphila$...) and restrain potentially harmful bacteria. These changes are «correlated» with the improvement of host health.
- All fractions do not produce the same effects on gut microbiota composition and host metabolism; some effects are unrelated to gut microbial changes.
Perspectives

• The diversity of nutrients with prebiotic properties in whole grain and bran (resistant starch, fructans, arabinoxylans, polyphenols...) create a complex « food for bugs” : it would be important to evaluate the advantage of mixing different compounds with prebiotic properties.

• To ensure good care of the diversity of bacterial functions by grain and bran products, it would be important to focus on metabolites prone to act on host physiology (metabolomics) in intervention studies trying to relate changes in gut microbiota with effects on host health.

• The choice of target population for intervention studies is important and related to the evolution of gut microbiota with age...
I think these are all conclusions. can you do anew slide for perspectives?
margaret; 14/10/2015
Evolution of microbiota composition with the age  
How to manage disease risk and health?

<table>
<thead>
<tr>
<th>Stage</th>
<th>Infancy</th>
<th>Early childhood</th>
<th>Childhood</th>
<th>Adolescence</th>
<th>Emerging adulthood</th>
<th>Adulthood</th>
<th>Retirement</th>
<th>Late senior</th>
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<tbody>
<tr>
<td>Host genetics</td>
<td>Developing immune system</td>
<td>Developing immune system</td>
<td>Greater socialization</td>
<td>Puberty</td>
<td>Frequent moving</td>
<td>Stable co-habitation</td>
<td>Aging</td>
<td>Advanced age</td>
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<tr>
<td>Delivery mode</td>
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Richness: High Stability: Stable  
Low Unstable

Figure part a is modified, with permission, from REF. 1 © (2010) US National Academy of Sciences.

A place for whole grain and bran products in a healthy food for gut microbes... and for us
Thanks to our collaborators: Guiot, G. Muccioli, JP Thissen, Ph.de Timary, Y. Larondelle, JB Demoulin (UCL), K. Verbeke (KUL), T VanDeWiele (Ugent), L. De Vuyst (VUB). Abroad: F. Backhed (Göteborg, Sweden), J. Walter (Canada), A Ramer-Tait (US), D. Langin (Toulouse, F), S. Claus (Reading, UK), K. Scott (Aberdeen, UK), W. DeVos (Wageningen, Netherlands), B. Pot (Lille, F)….