Acetate as metabolic target in the prevention of overweight-related chronic metabolic disorders

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Background

The gut microbiota has been suggested to be involved in the etiology of obesity and type 2 diabetes mellitus. Gut-derived short chain fatty acids (SCFA), formed by microbial fermentation of indigestible carbohydrates, might be involved in the control of body weight and insulin sensitivity *(Figure 1)*. We showed that acute infusions of the SCFA acetate in the amount achieved by a high fibre diet, in the distal, but not in the proximal part, of the colon increased circulating acetate, fat oxidation, peptide YY and slightly decreased TNF. Based on this study and the results of a follow-up study with colonic infusions of SCFA mixtures (*Figure 2*), we will explore the effects of specific dietary fiber mixtures on acetate levels in the distal colon and systemic circulation in relation to effects on the human insulin sensitivity.

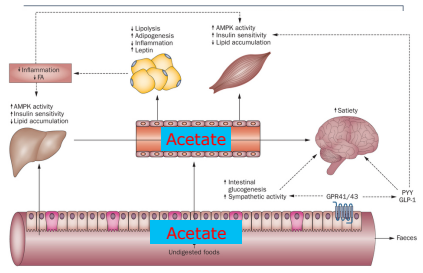


Figure 1: *SCFA in body weight control and insulin sensitivity. Adopted from Canfora et al. 2015 Nature Reviews Endocrinology.*

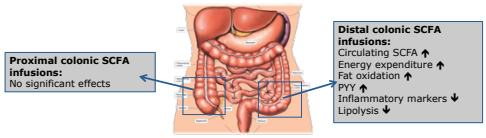
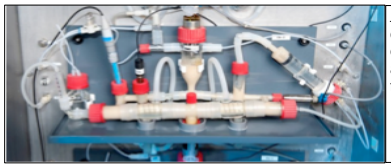


Figure 2: *Outcomes human intervention studies. Clinical science 2016, Scientific report 2017*

Objectives

Combine human physiological and cellular/molecular phenotyping with activity profiling and *in vitro* digestion models:

1. Define a high acetogenic fiber (mixture) *in vitro*

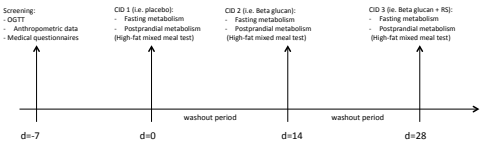


In vitro model of the human colon to select an optimal fiber mixtures

- Seven dietary fibers and mixtures with resistant starches have been tested for fermentation time and acetate production in TIM-2

2. To study the effect of fiber supplementation on acetate concentrations and substrate and energy metabolism *in vivo*

- Two acute double blind, placebo controlled randomized, crossover studies
- Twelve lean (BMI ≥ 20kg/m^2 ≤ 25kg/m^2) healthy men aged 30 – 65 years and 12 overweight/obese (BMI ≥ 25kg/m^2 ≤ 34.9kg/m^2) pre-diabetic men aged between 30 – 65 years



Example study design

Results *in vitro* study

- In total 11 fibers have been tested, of which 3 were readily available in commercial quantitites for the human intervention studies
- - Of the 3 eligible fibers the combination of long-chain inulin with resistant starch (*Figure* 3) and the combination of beta glucan with resistant starch (*Figure 4*) showed the highest increase in microbial acetate production in the distal colon (last 16 hours).

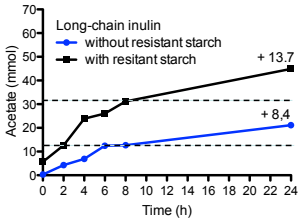


Figure 3: Long-chain inulin results

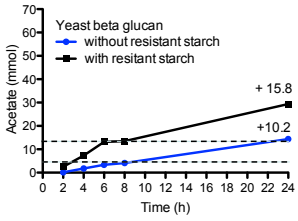


Figure 4: Yeast beta glucan results

Update *in vivo* study

- Based on *in vitro* results, a mixture of yeast beta glucan with/without resistant starches and long-chain inulin with/without resistant starches will be tested *in vivo*
- METC protocol accepted in January 2018
- Twenty-eight screenings done
- Fifteen participants included

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