SCFA production and their metabolic effects after inulin ingestion

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Based on our hypothesis that orally ingested inulin is fermented into different SCFAs, and these SCFAs can have beneficial metabolic effects, we aim to address the following primary objective: To investigate the human metabolic effects of SCFA...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON38942

Source
ToetsingOnline

Brief title
Inulin and SCFA production

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Lipid metabolism disorders

Synonym
impaired fat metabolism, Overweight

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Top Institute Food and Nutrition (TIFN)

Intervention

Keyword: Gut microbiota, Inulin, Metabolism, Short chain fatty acids

Outcome measures

Primary outcome

Primary endpoint:

Energy expenditure, fat and carbohydrate oxidation.

Secondary outcome

Secondary endpoints:

- 13C incorporation in SCFA from labelled inulin in peripheral blood and faeces;

- Plasma and fecal SCFA content after inulin ingestion;

- Hormones that influence substrate and energy metabolism like Insulin,

Glucagon, GLP-1, PYY, FIAF;

- Circulating metabolites like Glucose, Free Fatty Acids, Triglycerides;

- Inflammatory markers like TNF-α, IL-6, IL-1, Adipokines;

- Indirect markers of insulin sensitivity like circulating insulin

concentrations;

- Breath sampling for 13CO2;

- Adipose tissue and muscle gene/protein expression and inflammatory

markers;

- Appetite (VAS-scoring).

Study description

Background summary

The gut microbiota play an important role in metabolic diseases. One of the major roles of the gut microbiota is to ferment undigested food particles, for example resistant starch and carbohydrates, into SCFAs. The most abundant SCFAs are acetate, propionate and butyrate. SCFAs can have beneficial effects on body weight and insulin sensitivity, as is shown in several animal and human studies. Underlying mechanisms how SCFAs can influence metabolism still need to be unravelled.

An example of a fermentable carbohydrate is the prebiotic inulin, which occurs naturally in chicory-based products such as endive and radicchio. Prebiotics escape digestion and are fermented by bacteria in the gut. Inulin has been proven to produce SCFA in in vitro models in a ratio of 65:20:15 (acetate:propionate:butyrate). Most fermentation of inulin occurs in the proximal part of the colon, and our own research proves that increasing SCFA in the proximal part of the colon can have a beneficial effect on human substrate and energy metabolism, as can be seen by a significant lowering of plasma glucose and insulin 60 minutes after SCFA infusion in the colon.

Several studies examined the role of inulin on substrate and energy metabolism. Most studies focus on a chronic effect of 9-14 gram inulin supplementation for 4 to 8 weeks. A significant lowering of triglycerides was observed in several human studies. Lowering of insulin, lowering of fasting glucose, significant lowering of LDL-C and total cholesterol, and a significant decrease of body weight, BMI, and intake of energy and total fat was observed. A study in beagle dogs confirms that total energy expenditure measured in these dogs is significantly higher after an inulin-containing diet for 21 days. No direct measurements of energy expenditure after inulin ingestion in humans have been conducted so far. Inulin can also significantly increase the bifidobacteria, which are considered beneficial for human health due to their ability to increase butyrate formation.

Acute effects (< 8 hour) of 24 gram inulin include increasing plasma GLP-1 and decreasing plasma ghrelin in healthy human subjects. Also serum acetate, propionate and butyrate were significantly higher after inulin intake from 4-6 hours, with acetate peaking at 4.5h, propionate at 5h and butyrate at 5.5h. A study conducted in healthy and hyperinsulinemic volunteers showed a lower fasting and post-prandial serum SCFA concentrations in healthy volunteers after 24 gram inulin intake, however no difference in SCFA formation after inulin intake was found between the two groups. They also did not find any significant increase in plasma SCFAs 4h after inulin ingestion. A longer study period of 6-8h is needed to see the differences in SCFA production.

We hypothesize in the current study that inulin is fermented into different SCFAs, which are taken up by the colon, enter the blood stream and have beneficial signalling and/or direct metabolic effects.

Study objective

Based on our hypothesis that orally ingested inulin is fermented into different SCFAs, and these SCFAs can have beneficial metabolic effects, we aim to address the following primary objective: To investigate the human metabolic effects of SCFA derived from inulin.

Study design

This is a double-blind randomized placebo-controlled study.
After initial screening, the subjects come to the university for 3 testdays.
Each testday they will be provided with a high-fat mixed meal, and measurements will follow. Different products will be diluted into the high-fat mixed meal (see intervention: inulin, or maltodextrin). Each testday measurements via a ventilated hood will take place, next to blood sampling and breath sampling at different timepoints. At two of the three testdays, also muscle and fat biopsies will take place, one in the morning before intake of the mixed-meal and one at the end of the testday, totalling 4 fat biopsies and 4 muscle biopsies.

Intervention

In total there will be three test days with a wash-out period of one week in between. The interventions will be diluted into a high-fat milkshake.
The three test days consist of:
1. 13C inulin (500mg) + 23,5gram inulin
2. 24 gram inulin (as background for 13C inulin measurements)
3. 24 gram maltodextrin (placebo)

Study burden and risks

All subjects will be screened before participation and thereby receive information about their health status. In the future there can be general health benefits for the public, but the volunteers will have no personal benefits by participating in the study. The general interest of this study is that there have never been investigations with 13C labelled inulin combined with an oral inulin load in human beings. This is the first study where 13C label incorporation in venous plasma will be measured, and linked to metabolic responses after an inulin load.
There are different burdens volunteers can experience during the study. Burdens that volunteers can experience are the time spent with the study (subjects will have to invest approximately 27 hours in the study, divided among 3 days and a screening visit) and the dietary and healthy regimen they have to follow. Also the collection of fecal samples can be experienced as a burden for the volunteers, because they have to handle them their selves.
During the study, blood will be collected via a venous catheter. Venepunctures

can occasionally cause a local hematoma or bruise to occur. Some participants report pain during venepuncture. The total amount of blood sampled is 13x10mL per test day, totalling 390mL during the whole test period. The adipose tissue biopsy might cause local hematoma as well. Some participants report pain which is experienced as muscle pain after the muscle biopsy. More often the muscle feels stiff for a couple of days after the biopsy. To minimize the risk for a hematoma, the biopsy place will be compressed for approximately 5 minutes after biopsy. The place of incision will leave a small scar (3 mm for adipose tissue biopsy and 8 mm for skeletal muscle biopsy). To promote good wound healing, the incision will be sealed with sterile steristrips and a waterproof band-aid. The muscle biopsy will, in addition, be sealed with a compression bandage. For the indirect calorimetry, healthy volunteers have to lay on a bed for a couple of hours in a row, and this can be tiring. We try to reduce the invasiveness of the ventilated hood by using blocks of 25-50 minutes where the hood stays on. In between the blocks, the volunteers still need to lie on the bed, however the hood is off and they can get some fresh air. All other measurements, such as the breath samples and VAS-scoring cause no discomfort.
There have been few reports of side-effects after inulin ingestion. The effects reported were cramps and flatulence, however after chronic inulin intake for 2 months at an amount of 14 gram per day. Even dosages up to 40 gram of inulin per day caused no nausea or headache in obstipated patients. Bowel frequency was however increased, and four out of 25 patients complained about moderate abdominal pain at the high dosage of 40 gram for 7 days. At a dosage of 20 gram inulin per day, no side-effects were reported at all. No side-effects after a single oral dose of 24 gram inulin were reported in two different studies. The use of 13C labelled inulin is not considered as harmful. Inulin is a natural product and 1-2% of the C-atoms in natural occurring inulin are 13C-atoms. These 13C-atoms are stable and do not degrade into harmful products. The departments of Surgery and Human Biology have experience with the use of stable isotopes, even within the same TIFN project (METC 11-03-72).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Overweight/obese men (BMI>=25kg/m2<=35kg/m2)
- Aged 20 - 50 years
- Caucasian
- Normal fasting glucose (plasma glucose < 6.1 mmol/L)
- Normal blood pressure (systolic blood pressure 100-140mmHg, diastolic blood pressure 60-90 mmHg)
- Weight stable for at least 3 months (± 2kg)

Exclusion criteria

- Type 2 diabetes mellitus (defined as FPG >= 7.0 mmol/l)
- Gastroenterological diseases or abdominal surgery
- Cardiovascular diseases, cancer, liver or kidney malfunction, disease with a life expectancy shorter then 5 years
- Abuse of products
- Plans to lose weight or following of a hypocaloric diet
- Regular supplementation of pre- or probiotic products, use of pre- or probiotics 3 months prior to the start of the study
- Intensive exercise training more than three hours a week
- Use of any medication that influences glucose or fat metabolism and inflammation (i.e. NSAIDs).
- Regular use of laxative products
- Use of antibiotics 3 months prior to the start of the study

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-02-2014
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	23-12-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-05-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL45483.068.13
Other	Not yet assigned

Study results

Date completed:	07-07-2014
Actual enrolment:	15