The effects of differential SCFA availability on human substrate and energy metabolism

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Based on our hypothesis that differential availability of SCFA will have beneficial effects on substrate and energy metabolism, the following objectives will be addressed:In this pilot study we will validate whether rectal administration of SCFA is...

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

Summary

ID

NL-OMON37890

Source
ToetsingOnline

Brief title
SCFA administration and substrate and energy metabolism

Condition

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

Synonym
impaired fat oxidation, 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, insulin sensitivity, short-chain fatty acids, substrate and energy metabolism

Outcome measures

Primary outcome

The primary outcome parameters are fat oxidation and energy expenditure.

The impact of site of administration of SCFA on fat oxidation and energy

expenditure will be studied as well as the duration of effect.

Secondary outcome

- 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;

- Faecal and plasma SCFA content (Faecal samples only in pilot study);

- Indirect markers of insulin sensitivity like circulating insulin

concentrations;

- Appetite (VAS-scoring system).

Study description

Background summary

Gut microbiota is being increasingly recognized as an important factor in fat distribution, insulin sensitivity and glucose and lipid metabolism. Accordingly, the intestinal microbiota could play an important role in the development of obesity and type 2 diabetes mellitus. The role of gut-derived short-chain fatty acids (SCFA), the formation of which is enhanced by microbial fermentation of fibre, is still controversial. One study found that an increase in the formation of SCFA stimulated energy extraction from diet, with

subsequent weight gain. In contrast, supplementation of non-fermentable carbohydrates, which lead to an increase in SCFA formation, had beneficial effects on body weight control and insulin sensitivity. Of note, a study showed that butyrate supplementation in mice prevented diet-induced obesity and insulin resistance. At the present time, our understanding of the effects of SCFA on human metabolism (in gut or systemically) is still limited. Yet, in light of the health claims of certain dietary fibres (prebiotics), a detailed picture of the physiology of human SCFA metabolism and its interaction with the microbiome is of pivotal importance. We hypothesize that the differential availability of SCFA impacts human metabolism differently. To determine whether rectal administration of SCFA is a good model for studying the metabolic effects of SCFA we first perform this pilot study. In this pilot study we will determine if rectal administration of sodium acetate has the same effects on substrate and energy metabolism compared to proximal administration.
The total TIFN project will provide more insight into how increased availability of a beneficial SCFA mixture might serve as a basis for rational nutritional strategies in the prevention and treatment of obesity and type 2 diabetes mellitus.

Study objective

Based on our hypothesis that differential availability of SCFA will have beneficial effects on substrate and energy metabolism, the following objectives will be addressed:
In this pilot study we will validate whether rectal administration of SCFA is a good model for studying the acute metabolic effects of SCFA. For this, it will be investigated if site of administration (in distal or proximal colon) of sodium acetate differentially affects parameters of substrate and energy metabolism and to test the duration of short-term effects of sodium acetate administration on markers of substrate and energy metabolism.
When the model of rectal administration is a good model for studying sodium acetate metabolism, this will be applied later on in a short-term and long-term study. If not, we may have to use a model of proximal infusion in further studies.

Study design

After the screening visit, the subjects will come to the university 8 times in 15 days. During the first 4 days, the subjects will recieve an endoscopic procedure (sigmoidoscopy or colonoscopy, randomized) at which a catheter is clipped inside the colon distal or proximal to the flexura hepatica. The catheter is placed at the first day and will be in place for the next 3 days. After placement of the catheter, subjects will stay at the university and come to the laboratory 24, 48 and 72h after initial placement, for the test days. During the test days (each approximately 6h per test day), colonic infusions of sodium acetate 100mM, sodium acetate 180mM and placebo (0.9% saline infusion)

in a randomised order will take place. Via a 'ventilated hood' and blood sampling (10mL each sample) markers of substrate and energy metabolism will be examined. After the three test days, the catheter will be pulled out and a wash-out period of a week will follow. After the wash-out period, the subjects undergo a second endoscopic procedure (sigmoidoscopy or colonoscopy, depending on the first procedure), at which a catheter is clipped in the colon. After the endoscopic procedure, the subjects go home with the catheter in situ and come to the university at 24, 48 and 72h after initial placement of the catheter for the test days. During the test days, 100mM of sodium acetate, 180mM sodium acetate or placebo (0.9% saline) will be administered in a randomised order. Via a 'ventilated hood' and blood sampling from a distal arm vene, markers of substrate and energy metabolism will be monitored.

Intervention

Pilot study: All subjects will be studied 2 times, with once infusions in the proximal colon and once infusions in the distal colon in randomized order, each with three different infusions in randomized order consisting of:
1. Sodium acetate 100mM (0.984g sodium acetate dissolved in 120 ml water, isotonic)
2. Sodium acetate 180mM (1.772g sodium acetate dissolved in 120ml water, isotonic)
3. Placebo (0.9% NaCl in 120ml water)

Study 1: All Subjects will be studied 6 times with different combinations of SCFA and placebo enemas in randomized order (place of administration depending on outcome of pilot study).

Study 2: All subjects will be studied 3 times with the most promising SCFA or SCFA combinations and once a placebo enema in randomized order after 14 days of intervention.

Study burden and risks

Subjects will obtain during the screening visit general 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. They will, however, receive a financial contribution for participating in this study.
There are different burdens volunteers can experience during the study. Burdens that volunteers can experience are the time spend with the study (subjects will have to invest approximately 144 hours in the study) and the dietary and healthy regimen they have to follow. They have to follow the diet exactly as prescribed and cannot use alcohol during the test days. They also need to laxate the colon before coming for the endoscopic procedures, which can cause abdominal cramps and frequent toilet usage. The catheter, which will stay

inside the colon for three days in row, can cause interference with the normal daily structure of the volunteer. There will be a small part of the catheter hanging out of the rectum for infusion of the solutions; this can cause disturbances in daily life.
At this pilot 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. In addition, volunteers undergo a colonoscopy and sigmoidoscopy, which can lead to several complications and has several risks (complication rate: 2 in 1000 colonoscopies). In patients undergoing sigmoidoscopies and colonoscopies for medical reasons, there is a small (0.08%) risk of bowel perforation and bleeding at the biopsy sites. This risk is expected to be much smaller in the present study, because no severely ill subjects will be recruited. Complications mainly appear after removal of polyps. A report of the *gezondheidsraad* mentions a risk of 0.0025% risk of perforation after screening for cancer in healthy subjects. Some participants report pain or unpleasant feelings during the endoscopy. Patients will be sedated with Midazolam (5mg/mL), 2 - 2.5mg during the colonoscopy, but not during the sigmoidoscopy. Sedative agents can cause respiratory depression, hypoxia and hemodynamic effects. The risk of these complications is relatively small and patient*s saturation, heart rate and respiratory rate will be monitored during the procedure. In the gastroenterology department there is a lot of experience with these procedures and they are also used in daily clinical practice. During the proximal placement of the catheter, intermittent fluoroscopy will be used to ascertain that the catheter is still positioned correctly. The radiation exposure during the retraction of the endoscope is minimal (0.06 mSv), which equals less then 10% of normal annual background radiation.

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 (NGT: 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:	Observational invasive
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-05-2012
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO Date:	07-03-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-05-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-09-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-11-2012

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	NL38679.068.11