The effects of rectal administration of SCFA on human substrate and energy metabolism

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

Summary

ID

NL-OMON38741

Source
ToetsingOnline

Brief title
rectal SCFA administration and substrate and energy metabolism

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, 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;

- plasma SCFA content

- 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 have performed a pilot study (METC 11-3-079, NL38679.068.11). In the study we have determined if rectal administration of sodium acetate has the same effects on substrate and energy metabolism compared to proximal administration. Our results indicate that the primary outcome parameter fat oxidation was significantly changed, when sodium acetate 180mM was administered in the distal part of the colon (see objectives). In contrast, no effect on our first outcome parameters were seen, when sodium acetate was administered in the proximal colon. Consequently, we will administer the SCFA in this short-term study rectally by using enemas.
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. To obtain rational nutritional strategies, a next step in this TIFN project will be focused on dietary ingredients modulating intestinal microbiota and subsequent SCFA production.

Study objective

Based on our hypothesis that differential availability of SCFA will be beneficial effects on substrate and energy metabolism, the following objectives have been and will be addressed:
- In our previous study (METC 11-3-079, NL38679.068.11) we have validated whether rectal administration of SCFA is a good model for studying the acute metabolic effects of SCFA. For this, we have investigated if site of administration (in distal or proximal colon) of sodium acetate differentially affects parameters of substrate and energy metabolism

and we have tested the duration of
short-term effects of sodium acetate administration on markers of substrate and energy metabolism.
Analyses of our primary outcome parameter fat oxidation showed an 23% increase in fat oxidation area under curve (AUC) of the first 2h basal period (significant, p=<0.05), when the high concentration (180mM) sodium acetate solution was infused distally, compared to placebo.
Proximally, we did not find significant differences in any of our primary outcome parameters. This data indicated that
rectal infusion is a good model to study metabolic effects of SCFA. Thus, we will use in this study enemas to
administer the SCFA.
Based on our hypothesis that differential availability of SCFA will have beneficial effects on substrate and energy
metabolism, the following objectives will be addressed:
- to investigate short-term effects SCFA combinations by rectal administration on markers
of substrate and energy metabolism during overnight fasted conditions and after a glucose load.
With the most promising SCFA combinations found in this short-term study , we will perform a longer
term study (14 days) investigating its effects on insulin sensitivity and markers of substrate and energy metabolism in
overweight subjects.

Study design

After the screening visit, the subject will come to the university 4 times in 21 days. During the test day (each
approximately 6h per test day), rectal infusion of a 200mL solution with a combination with sodium acetate 24mmol, sodium butyrate
8mmol and sodium propionate 8mmol, a combination with sodium butyrate 14mmol, sodium acetate 18mmol and sodium propionate 8mmol, a combination with sodium propionate 14mmol, sodium acetate 18mmol, sodium butyrate 8mmol or a placebo (saline infusion, 40mmol NaCl) in a randomized will take place. Via a 'ventilated hood' and blood sampling markers of substrate and energy metabolism will be examined.

Intervention

During the test day (each approximately 6h per test day), rectal infusion of a 200mL solution with a combination with sodium acetate 24mmol, sodium butyrate 8mmol and sodium propionate 8mmol, a combination with sodium butyrate 14mmol, sodium acetate 18mmol and sodium propionate 8mmol, a combination with sodium propionate 14mmol, sodium acetate 18mmol, sodium butyrate 8mmol or a placebo (saline infusion, 40mmol NaCl) in a randomized will take place. The infusions

will be given twice per test day, in post absorptive conditions and after a glucose load.

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. They will, however, receive a financial contribution for participating in this study. The general interest of this study is that there have never been human intervention studies with the SCFA butyrate, propionate and the combinations we will investigate, and their effects on the human substrate and energy metabolism. The concentrations of acetate, propionate and butyrate that will be reached in the study resemble the concentrations that are reached with a high dietary fibre diet and are thus within the high physiological range. For detailed information see paragraph 5.
After initial screening, subjects will have to invest approximately 24 hours in the study. 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.. In the study enemas will be used. The procedure of the rectal infusion can be a burden for the volunteers and can be experienced as an embarrassment. During the enema administration, the coordinating investigator will take care of the privacy of the volunteers. Enemas are clinically used for several purposes, for example to remove faeces when an individual is constipated, to cleanse the rectum as preparation for an endoscopic examination, or to administer drugs or anaesthetic agents. Enemas differ greatly in volume (3 ml - 1 L) depending on the area of the colon that has to be reached by the fluid. In the present study 200 ml enemas will be used. During the enema administration, the coordinating investigators will take care of the privacy of the subjects. There is a small risk of rectum perforation when using enemas. In other study no irritation, consecutive bowel movements or other side effects due to enemas administered in a higher volume per minute were reported. Also, in the department of gastroenterology studies were performed where the volunteers insert enemas twice daily for ten days, and reported no irritations. These studies were approved by the METC (MEC 06-3-067, MEC 06-3-020, MEC 06-3-071).

Contacts

Public
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL
Scientific
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-09-2013
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO

Date:	24-07-2013
Application type:	First submission
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	NL44507.068.13

Study results

Date completed:	10-01-2014
Actual enrolment:	13