Human short chain fatty acid metabolism and microbiota

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Knowledge about the physiological metabolism of SCFAs and the interorgan exchange of SCFAs across different abdominal organs in humans is lacking to some extent.To this end, the following objective will be addressed in the current study: -Determine...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON37878

Source
ToetsingOnline

Brief title
Human SCFA metabolism

Condition

- Other condition
- Appetite and general nutritional disorders

Synonym
Obesity

Health condition

Obesitas

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Energy balance and metabolism, Microbiota, Short chain fatty acids

Outcome measures

Primary outcome

The primary study parameter is the plasma concentration of the SCFAs acetic

acid, propionic acid and butyric acid in human measured using High Performance

Liquid Chromatograpy (HPLC-MS).

Secondary outcome

Other study parameters:

Duodenal biopsy: SCFA- receptors GPR41 and GPR43, hormones that influence

substrate and energy metabolism (GLP-1, PYY), metabolites (FIAF).

Liver biopsy: markers for substrate, energy and/or cholesterol metabolism;

glucose 6-phosphate, SREBP-1 expression,

Study description

Background summary

Recent evidence suggests that gut microbiota play a major role in the pathophysiology of obesity and its related disorders. Data points towards the existence of quantitative and qualitative differences in gut microbiota between lean and obese and between diabetic and non-diabetic individuals. These distinct differences in gut microbiota have been suggested to influence the

energy extraction of ingested foods, intestinal permeability and transit time, mucosal immunity and systemic inflammation and as such, may play an important role in the development of obesity and its related disorders. In line with this, germ-free mice are protected from obesity when fed a high-fat Western diet. Apparently, germ-free mice are devoid of short chain fatty acids (SCFA), indicating the importance of gut microbiota providing products that affect host metabolism.
However, a detailed understanding of the SCFA metabolism and the interorgan exchange of SCFA in vivo in humans is lacking, and the relation gut microbiota-host metabolism remains largely unclear.

Study objective

Knowledge about the physiological metabolism of SCFAs and the interorgan exchange of SCFAs across different abdominal organs in humans is lacking to some extent.
To this end, the following objective will be addressed in the current study:

-Determine in vivo in humans the role of different abdominal organs in the production or extraction of SCFAs

To assess SCFAs handling of individual organs, we will once sample 10 ml blood from the above indicated blood vessels during surgery and then we will make use of a recently validated, highly accurate HPLC-MS method to determine concentrations of the SCFAs acetic acid, propionic acid and butyric acid in human plasma samples34. Additionally, 1 liver and 1 duodenal biopsy will be taken allowing detailed study of SCFA metabolism in the gut-liver axis in vivo in humans.

* We hypothesize that intestinal butyric acid and proprionate release by the gut is equaled by hepatic uptake of these SCFAs
o We hypothesize that the net organ fluxes of butyric acid and proprionate will indicate release of these SCFAs by the gut
o We hypothesize that the net organ fluxes of butyric acid and proprionate will indicate uptake of these SCFAs by the liver

* We hypothesize that the net organ fluxes of the SCFAs across the colon will be higher compared to the net organ fluxes of these SCFAs across the small intestine pointing out the colon as the dominant part of the gut in producing these SCFAs
* We hypothesize that the net organ flux of acetic acid across the liver will be close to zero indicating no significant uptake/release of acetic acid by the liver
* We hypothesize that the concentration of acetic acid in the hepatic vein will be lower compared to the concentration of acetic acid in the arterial radialis indicating peripheral absorption

Study design

This is a cross-sectional descriptive study.
For this study, patients undergoing pp Whipple will be recruited at the surgical outpatient clinic of Maastricht University Medical Center (MUMC+). First, patients will consult their surgeon for the so called *preoperative screening*. This screening is intended to determine whether and what kind of operation is suitable for the patient involved. In case the surgeon assumes that a patient may be suitable for participation in this study, he will briefly cite the study. Once the patient has indicated to be willing to receive more information about this study, the researcher will be informed by the surgeon. Subsequently, the researcher will check in a consult with the patient immediately following the preoperative screening, if he/she is indeed suitable for participation in this study on the basis of the inclusion and exclusion criteria as described below. During this consult, patients are given the opportunity to ask questions. Afterwards, the patients go home with the written information as provided by the researcher. Should they encounter questions, they always can contact the researcher to ask questions. In addition, it is possible to contact an independent medical doctor. Finally, the day of admission, generally one day before surgery, there is again time to ask questions. If the patient decides to participate in the study, informed consent will be obtained. Subjects are participating entirely voluntarily in this study and can stop their participation at any time for any reason if they wish to do so without any consequences.
From the patients participating in the study blood samples will be collected. Blood will be sampled from the portal vein, hepatic vein, superior mesenteric vein, inferior mesenteric vein, splenic vein, renal vein and the radial artery according to Figure 1. Arteriovenous differences (ΔAV) and net organ fluxes (flow x ΔAV) are a quantitative measure of the role of the liver, PDV, the splanchnic area, small intestine, colon, spleen and the kidneys in producing or extracting SCFAs.

All patients undergoing pp Whipple have an arterial catheter during surgery from which we can sample blood. The mentioned veins will be punctured directly using 25G needles as described previously in several MEC protocols and in a publication of Van de Poll et al (MEC 02-045, MEC 03-032, MEC 06-2067 and [35]). Only once 10 ml of arterial blood and 10 ml intra-abdominal blood from the different vessels separately will be sampled resulting in a total amount of maximal 70 ml. All blood samples will be collected in both pre-chilled EDTA and heparinized vacuum tubes and thereafter centrifuged at 3500 rpm at 4°C for 10 minutes. Plasma will be stored in Eppendorf cups at -80°C until further analysis. Blood flow will be measured using intra-operative Duplex ultrasonography and the concentration of the SCFAs acetic acid, propionic acid and butyric acid in human plasma samples will be measured using HPLC-MS as previously described34. Additionally, 1 liver and 1 duodenal biopsy will be taken allowing detailed study of SCFA metabolism in the gut-liver axis in vivo

in humans. The methods applied, i.e. intra-abdominal blood sampling and collecting liver biopsies, have been previously used without any problems for the surgical procedures or the patients. Besides, there are no additional risks to the collection of duodenal biopsies since these are part of the duodenum which is resected anyway.

The corresponding AV differences will be calculated as follows:
ΔAV PDV = [PV] - [A]
ΔAV Splanchnic area = [HV] - [A]
ΔAV IMV = [IMV] - [A]
ΔAV SMV = [SMV] - [A]
ΔAV SV = [SV] - [A]
ΔAV RV = [RV] - [A]

Fluxes will be calculated as follows:
F PDV = portal plasma flow*([PV]-[A])
F Splanchnic area = splanchnic plasma flow*([HV] - [A])
F Liver = F splanchnic - F PDV
F Colon = inferior mesenteric plasma flow*([IMV] - [A])
F Small intestine = superior mesenteric plasma flow*([SMV] - [A])
F Spleen = splenic plasma flow*([SV] - [A])
F Kidneys = renal plasma flow*([SV] - [A])

ΔAV = Arteriovenous differences
PDV = Portal drained viscera
A = Blood sample from arterial line
PV = Blood sample from portal vein
HV = Blood sample from hepatic vein
IMV = Blood sample from inferior mesenteric vein
SMV = Blood sample from superior mesenteric vein
SV = Blood sample from splenic vein
RV = Blood sample from renal vein

Of note, positive fluxes indicate release, whilst negative fluxes indicate uptake.

Study burden and risks

The methods applied, i.e. intra-abdominal blood sampling and collecting liver biopsies, have been used previously without any problems for the surgical procedures or the patients (MEC 02-045, MEC 03-032, MEC 06-2067) as published by Van de Poll et al. Besides, there are no additional risks to the collection of duodenal biopsies since these are part of the duodenum which is resected anyway.

Although the results of this project have no direct positive effects for the patients involved, they do contribute to the understanding of the SCFA metabolism, and thereby form a basis in the process of unraveling the relation between gut microbiota, SCFAs and human energy and substrate metabolism. Future nutritional modulation of gut microbiota may beneficially affect gut and host health.

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

Patients undergoing pylorus preserving pancreactico duodenectomy
18 < Age < 75 years old

Exclusion criteria

Ileo- or colostomy
Parenchymal and/or inflammatory liver disease
Steroid hormone medication
n-acetyl cystein medication
Lactation, pregnancy and planning of pregnancy
Inflammatory bowel disease
Coagulation disorders
Excessive drinking (>20 alcoholic consumptions per week) and/or smoking
Inborn errors of metabolism (liver enzyme deficiencies)
Use of antibiotics during and 3 months prior to the study
Pre-and probiotic use during and 3 months prior to the study

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-06-2012
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	02-04-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	14-11-2012
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	NL39013.068.11