Acylcarnitine and insulin resistance: does y-butyrobetaine enhance fatty acid oxidation and influence acylcarnitine profiles?

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Primary: In this pilot study, we want to investigate the effect of y-butyrobetaine on free carnitine levels and acylcarnitine profiles in lean and obese subjects after oral administration of y-butyrobetaine. Secondary: to examine if FAO is enhanced...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON36950

Source
ToetsingOnline

Brief title
AIR-study: y-BB

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
insulin insensitivity, Insulin resistance

Health condition

Obesitas

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Acylcarnitines, Insulin resistance, Obesity, y-butyrobetaine

Outcome measures

Primary outcome

- Free carnitine levels (before/after y-BB administration)

- Acylcarnitine profiles (before/after y-BB administration)

Secondary outcome

- Fatty Acid oxidation rate (before/after y-BB administration)

- Insulin sensitivity (before/after y-BB administration)

Study description

Background summary

The Western lifestyle and concurrent obesity are the main causes of the strongly increasing incidence of type 2 Diabetes Mellitus, a condition characterized mainly by decreased insulin sensitivity of liver and skeletal muscle. It is suggested that insulin sensitivity is caused by disturbed fatty acid oxidation (FAO) due to high lipid burden in obese humans, a concept known as lipotoxicity.
In order to be oxidized, fatty acids need carnitine to pass the mitochondrial membrane. Together they form acylcarnitines, which are transported from the cytosol into the mitochondrion for further oxidation. Several relations between insulin resistance and acylcarnitines are studied and described. For example, acylcarnitines correlate negatively with insulin sensitivity. It is hypothesized that relative carnitine deficiency might contribute to mitochondrial dysfunction and obesity-related impairments in glucose tolerance. Indeed, insulin dependent type 2 diabetes mellitus patients have lower (~25%)

carnitine concentrations. Although it is currently unclear whether insulin resistance impairs FAO or impaired FAO contributes to insulin resistance, it is possible that carnitine supplementation improves insulin sensitivity and decreases lipid deposition in liver and muscle tissue. Supplementation with oral carnitine is probably of limited effectiveness, as carnitine uptake in the liver is low due to the low expression of the carnitine transporter OCTN2 in liver. In contrast, y-butyrobetaine is taken up very easily in liver and almost directly converted to carnitine, and administration of y-butyrobetaine significantly increases tissue carnitine concentrations. We hypothesize that enhancing the FAO rate by administering the carnitine precursor y-butyrobetaine, might decrease fat content in liver and subsequently improve hepatic insulin sensitivity. Additionally this could improve insulin sensitivity in muscle tissue as well.

Study objective

Primary: In this pilot study, we want to investigate the effect of y-butyrobetaine on free carnitine levels and acylcarnitine profiles in lean and obese subjects after oral administration of y-butyrobetaine.
Secondary: to examine if FAO is enhanced by administration of y-butyrobetaine, and if this increased FAO rate leads to changes in insulin sensitivity.

Study design

STUDYDAY 1
Before y-butyrobetaine administration starts, subjects will be fasted overnight, an REE will be performed in order to measure the contribution of fatty acid oxidation to total energy expenditure, and blood will be drawn (to measure y-butyrobetaine and free carnitine levels, acylcarnitine profiles, lipid profiles and glucose level). Then subjects will be asked to take 37.5mg/kg y-butyrobetaine.

STUDYDAY 2 to 14
On day 2 to 14, volunteers are asked to take one daily dose of y-butyrobetaine. On day 2,3 and 8, the volunteers come to the AMC in a sober state for blood withdrawal.

STUDYDAY 15
On day 14 another overnight fast is performed, followed again by an REE and blood withdrawal on day 15.

Intervention

Administration of an oral dose of the nutritional supplement y-butyrobetaine, for 14 days on a daily basis.

Study burden and risks

We believe that the risks and burden for the participants of the REE, blood withdrawal and y-butyrobetaine administration are minimal.

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

1- Healthy lean and obese (BMI 19-25 kg/m2 and >30 kg/m2 respectively) volunteers
2- Adult age (>18 years of age)
3- Normal liver and renal function
4- Informed consent

Exclusion criteria

1- Treated diabetes
2- HbA1c >8%
3- Any medication interfering with insulin sensitivity (steroids, beta-blockers)
4- Intensive sports (> three times weekly intensive training)
5- Any medical disorder of significant relevance
6- DM II in first degree family members
7- Hypertriglyceridemia or any other lipid metabolism disorder

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-04-2013
Enrollment:	4
Type:	Actual

Ethics review

Approved WMO

Date:	03-04-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL42247.018.12