

The effect of fasting-induced insulin resistance on brown adipose tissue activity, non-shivering thermogenesis and skeletal muscle mitochondrial uncoupling.

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The primary objectives of this study are: 1) To determine the effect of fasting-induced insulin resistance on cold-induced glucose uptake in brown adipose tissue; 2) To determine the effect of fasting on non-shivering thermogenic capacity; 3) To...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39127

Source

ToetsingOnline

Brief title

Effect of insulin resistance on brown adipose tissue activity.

Condition

- Other condition

Synonym

na

Health condition

Geen

Research involving

Human

Sponsors and support

Primary sponsor: Universiteit Maastricht

Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: Brown adipose tissue, Insulin resistance, Thermogenesis

Outcome measures

Primary outcome

The main study parameters are:

- Standard uptake value (SUV) of BAT: This is used as a measure of BAT glucose uptake and BAT activity and will be measured by means of FDG-PET/CT scanning.
- Skeletal muscle mitochondrial respiration/uncoupling: This will be determined in skeletal muscle samples using the Oroboros 2k Oxygraph instrument present in our laboratory.
- Energy expenditure: This will be measured by means of indirect calorimetry using a ventilated hood.
- Ex vivo skeletal muscle glucose oxidation: This will be measured to determine insulin sensitivity. A glucose oxidation assay with insulin stimulation will be performed in skeletal muscle biopsies.

Secondary outcome

Secondary study parameters include:

- Body temperatures: Skin temperatures will be measured by means of iButtons and core temperature will be determined by ingestion of a telemetric pill.
- Skin perfusion: This will be measured by means of LaserDoppler flowmetry.

- Blood parameters: Venous blood will be drawn by means of a catheter placed in the antecubital vein of the underarm. By using radioimmunoassay and high performance liquid chromatography blood parameters will be analyzed.
- UCP-1 and beta3-receptor polymorphisms

Study description

Background summary

Obesity and type 2 diabetes have emerged as two of the leading health problems in modern western society. So far, simple non-surgical treatment strategies for 'diabesity' are very often ineffective. A promising new target for increasing energy expenditure, and thus inducing weight loss, is facultative thermogenesis (i.e. heat production when needed, e.g. in the cold) through the activation of brown adipose tissue (BAT). Recently, we have shown a negative correlation between BAT activity upon mild cold exposure and body mass index (BMI), suggesting that BAT might play a significant role in the development and/or sustainability of obesity. Next to obesity per se, several animal studies and retrospective human studies have suggested that diabetic status or insulin resistance, the most important physiological hallmark of type 2 diabetes, also contribute significantly to cold-intolerance and reduced BAT activity. However, no prospective studies so far have investigated the role of insulin resistance in BAT activity upon mild cold exposure. In addition to BAT, skeletal muscle is also suggested to play a role in non-shivering thermogenesis (NST), through the process of mitochondrial uncoupling.

Study objective

The primary objectives of this study are: 1) To determine the effect of fasting-induced insulin resistance on cold-induced glucose uptake in brown adipose tissue; 2) To determine the effect of fasting on non-shivering thermogenic capacity; 3) To determine the effect of fasting on skeletal muscle mitochondrial uncoupling and how this is related to non-shivering thermogenesis.

Study design

The study will include 2 PET/CT scans for each individual, in which cold-induced BAT activity will be measured: the first scan will be performed after a normal-fed period and the second scan will be performed after a 54-h fasting period (to induce insulin resistance). Both scanning protocols consist

of a dynamic and static PET/CT scan. To investigate the role of mitochondrial uncoupling in skeletal muscle in cold-induced thermogenesis, muscle biopsies will be taken in both conditions. Thermogenesis will be measured using indirect calorimetry and the insulative response will be determined by thermometry and skin perfusion.

Intervention

Fasting period of 54 hours to induce severe insulin resistance in healthy subjects. The insulin resistance is temporarily and fully reversible.

Study burden and risks

The risks of this experiment will be low.

The total exposure to radioactive radiation due to the administration of ^{18}F -FDG for the PET/CT scans is 6,4 mSv for the total study. This is equal to about 3 times the total annual background radiation in the Netherlands and is considered as a low risk and fully acceptable for medical scientific research by the International Commission on Radiological Protection (<10 mSv). Thus, the risk of health damage is very limited.

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

Healthy, lean (BMI 18-25 kg/m²) adults

Age: 18-30 years

Male and female

For females: use of a specific oral contraceptive (Microgynon 30 or levonorgestrel/ethinylestradiol)

Caucasian

Sedentary (= < times/week or = < 3 hours/week sports)

Exclusion criteria

Cardiovascular diseases

Hypertension (systolic/diastolic blood pressure > 140/90)

Hypotension (systolic/diastolic blood pressure < 90/60)

Use of beta-blockers

Asthma or other obstructive pulmonary diseases

Diabetes Mellitus type 1 and type 2

Elevated blood glucose levels (>5.6 mmol/l)

Hyperthyroidism

Pregnancy

Participation in earlier research or medical examinations that included PET/CT scanning

Radiation therapy due to medical treatment

Unstable body weight (weight gain or loss >3kg in the past 2 months)

Any known or suspected obstructive disease of the gastrointestinal tract, hypo motility disorders of the gastrointestinal tract or previous gastrointestinal surgery.

Study design

Design

Study type: Interventional

Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL	
Recruitment status:	Pending
Start date (anticipated):	01-05-2012
Enrollment:	18
Type:	Anticipated

Ethics review

Approved WMO	
Date:	07-05-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	
Date:	11-04-2013
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
Other	Nederlands Trialregister: TC = 3523
CCMO	NL39816.068.12