Nutrient sensing in response to starvation in obese and lean individuals

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1. To compare the effects of fasting on energy sensing machinery in muscle of obese vs normal weight subjects2. To compare neuronal activity in the brain in response to fasting in obese vs normal weight humans3. To compare the activity of the HPA...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolism disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON34778

Source
ToetsingOnline

Brief title
Starvation and nutrient sensing

Condition

- Metabolism disorders NEC

Synonym
Obesity

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum
Source(s) of monetary or material Support: CMSB,industrieel geld uit ander(e) project(en)

Intervention

Keyword: AMPK, Energy-Sensing, Obesity, Starvation

Outcome measures

Primary outcome

Activity of energy sensing machinery, measured from muscle biopsies

HPA axis activity, measured by blood sampling

HPT axis activity, measured by blood sampling

Resting-state networks in the brain, measured by FMRI

MRI volumetric measurements of amygdale and hippocampus

Fat and glucose oxidation rates measured by indirect calorimetry

Secondary outcome

NA

Study description

Background summary

Supply of fuel is of critical importance for survival. Evolution therefore provided highly conserved, sensitive cell autonomous and systemic *energy gauges* to guard adequate availability of fuel. AMP activated protein kinase (AMPK) plays a pivotal role at the cellular level. It is activated by nutrient deprivation via a reduced intracellular ADP/AMP ratio and a variety of endocrine cues (including insulin and leptin) and controls energy balance by shutting off energy consuming processes while activating the machinery to produce ATP (1). The sirtuins are a family of highly conserved nicotinamide adenosine dinucleotide (NAD)+ dependent deacetylases that play similar roles by histone modification of genes encoding proteins involved in energy metabolism (2). Energy sensing neurons in the brain employ the same molecular machinery (AMPK in particular) to sense the body*s energy status and coordinate a multifaceted systemic neuroendocrine and behavioural response to nutrient deprivation. Most of these neurons are located in the hypothalamus and the nucleus of the solitary tract in the brain stem. They (in)directly control autonomic nervous system activity and pituitary hormone release to adapt

metabolism, and higher cortical neural circuits to regulate appetite (3).
Within this framework, the hypothalamus-pituitary-adrenal (HPA) and -thyroid (HPT) axes are particularly important for the control of energy balance and metabolism.
Obesity is marked by an altered setting of energy balance. It is extremely difficult to lose weight on a long term basis, as evidenced by the very disappointing results of virtually every weight loss strategy that has been developed in the last 50 years or so. Indeed, even after bariatric surgery almost no obese patient ends up with a normal bodyweight (although considerable amounts of weight are lost after these procedures). The above-mentioned energy sensing system probably underlies this difficulty. We propose that the setting of this system is different in obese humans. We specifically hypothesize that the molecular and systemic response to calorie restriction is more explicit in obese compared to normal weight individuals to explain there propensity to grow obese. To test this hypothesis we will map the integrated molecular and neuroendocrine response to fasting in obese vs normal weight humans. Muscle and brain are exquisitely sensitive to fuel deprivation. Therefore, we will study the (molecular) physiology of calorie restriction in these tissues. As endocrine systems are dynamic by nature, multiple sequential blood samples will be drawn to evaluate the status of the pituitary adrenal- and thyroid axes as pivotal components of the systemic neuroendocrine response.

Study objective

1. To compare the effects of fasting on energy sensing machinery in muscle of obese vs normal weight subjects
2. To compare neuronal activity in the brain in response to fasting in obese vs normal weight humans
3. To compare the activity of the HPA and HPT axes in response to fasting in obese vs normal weight humans
4. To determine the effects of weight loss on energy sensing in obese humans

Study design

All participants will be screened prior to this intervention study. There will be two groups in this study; lean and obese individuals.

All participants will be admitted to the clinical research unit of the department of internal medicine for a 60 hour fast. The lean individuals serve as a control group. Anthropometric measurements, a bioelectrical impedance analysis (BIA) and indirect calorimetry will be performed. A basal blood sample will be taken and a heart rate variability measurement will take place. Then a structural MRI and resting-state FMRI will be performed on a 3T MRI scanner. MRI scanning will take approximately 40 minutes. After MRI scanning a muscle biopsy will be taken from the musculus vastus lateralis.
Subsequently subjects will be fasted for a total of 60 hours after which the

anthropometric measurements, the BIA, the indirect calorimetry, the blood sampling, the heart rate variability, the MRI scan and the muscle biopsy will be repeated.
Thereafter the obese participants will use a very low calorie diet (VLCD, Prodimed) for 8 weeks to lose a substantial amount of weight. To monitor side effects, participants will be seen and/or phoned on a regular basis. We will see them after weeks 1, 2, 4 and 6 and phone them after weeks 3, 5 and 7. After the very low calorie diet, all procedures described above will be repeated, but the subjects will not fast.

Study burden and risks

The muscle biopsy regularly results in a hematoma and/or muscle ache at the place of the biopsy. The first 2 days after the biopsy, patients can experience a heavy feeling in the muscle.

From the use of Prodimed little side effects are expected. The most frequent occuring side effect during the use of Prodimed is obstipation, which can be released by increasing water intake. If this does not help, lactulose can be used.

There is a risk that unexpected findings will occur on the MRI scans. These will always be communicated to the patient and his/her general practioner. If a patient does not want to be informed about eventual unexpected findings, he or she will be excluded from participation in this study.

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 males and females
Age 19-60 yrs
Obese subjects: BMI >30 kg/m2
Lean controls: BMI 19-25 kg/m2
Stable weight for the last 3 months
Caucasian
FPG < 6 mmol/L
Hb > 7.5 mmol/l
Negative family history of DM2 (first degree family members)

Exclusion criteria

Use of medication known to affect glucose and/or lipid metabolism
History of genetic or psychiatric disease that affects the brain
Significant chronic disease
Renal or hepatic disease
Pregnancy
Smoking (current)
Alcohol consumption of more than 28 units per week at present or in the past
Recent blood donation (within the last 3 months)
Recent participation in other research projects (within the last 3 months), participation in 2 or more projects in one year
Contra-indication to MRI scanning

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2010
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO

Date:	02-06-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL30936.058.10