Brown adipose tissue after vagus nerve stimulation

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Primary Objective: To study the effect of VNS on BAT activity.Secondary Objective(s): Measure the effect of VNS on energy expenditure, core temperature, skin surface temperature and skin perfusion during active and absent stimulation.Follow the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Appetite and general nutritional disorders
Study type	Interventional

Summary

ID

NL-OMON38162

Source
ToetsingOnline

Brief title
Brown adipose tissue after vagus nerve stimulation

Condition

- Appetite and general nutritional disorders

Synonym
brown fat, obesity

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W,NWO TOP

Intervention

Keyword: brown adipose tissue, obesity, vagus nerve stimulation

Outcome measures

Primary outcome

The main endpoint of this study is BAT activity in kBq after active VNS.

Secondary outcome

Secondary endpoints are the effect of VNS on energy expenditure, body core temperature, skin surface temperature, skin perfusion and food intake.

Other study parameters

Other relevant study parameters are medical history, medication, current medical status, age, body weight, weight history, height, sex, thyroid gland function, and UCP-1 and beta3-receptor polymorphisms.

Study description

Background summary

Obesity is reaching endemic proportions in our Western society. It is now categorized as a chronic disease that is associated with severe comorbidities as hypertension, type II diabetes and cancer. During the last decades research in possible therapies for existing obesity and developmental factors causing obesity has explosively increased. Recently renewed interest aroused in brown adipose tissue (BAT), a tissue playing a possible role in both development and therapy for obesity. BAT is active in adult man, but is decreased in activity when body mass index (BMI) increases.
Many rodent studies report several active pathways for BAT activation, that is highly innervated and vascularised. Stimulation of sympathetic beta-receptors on BAT was already suggested to be a possible target for obesity several years ago. Interestingly, stimulation of the cervical part of the vagus nerve (=

vagus nerve stimulation (VNS)) generates weight loss in rodents. Furthermore, weight loss has been reported as a side-effect of VNS in humans, where it is successfully to treat medically refractory epilepsy. Other studies show effective weight loss applying a therapy that blocks the vagus nerve on the abdominal level. Since the vagus nerve has both strong afferent and efferent fibres, the vector of effect that induces weight loss is still unknown. Moreover, the effect of blockage or stimulation of the vagus nerve rests on the variation of the electrical pulse that has a certain amplitude and frequency. Unfortunately, the level and characteristic of this pulse causing either blockage or stimulation is not defined. The effect is only assumed to hypothetically block or stimulate. Thus, the described blocking could be stimulation and stimulation blockage. Nevertheless, this literature suggests electric pulsing of the vagus nerve is accompanied by weight loss. Recent studies report vagally mediated stimulation and suppression of BAT activity. Increased BAT activity can increase energy expenditure and cause weight loss. VNS and subsequent BAT activation could be a possible target in obesity. To define the relation between BAT and VNS, we set up the following research protocol. In this protocol BAT activity will be determined in subjects with stable, completed VNS for epilepsy. We hypothesize that BAT activity increases in VNS.

Study objective

Primary Objective:

To study the effect of VNS on BAT activity.

Secondary Objective(s):

Measure the effect of VNS on energy expenditure, core temperature, skin surface temperature and skin perfusion during active and absent stimulation.

Follow the postoperative weight changes of the study population (this is a retrospective objective)

UCP-1 and beta3-receptor polymorphisms.

Study design

In this study BAT activity is analyzed during active and absent VNS. Measurements will be performed in a cohort of epilepsy patients that is already treated with VNS. In these patients VNS consists of chronic cyclic electrical stimulation of the left vagus nerve by a subcutaneously placed pulse generator . The electrical pulses are transmitted by a helical bipolar electrode that is connected to the vagus nerve . BAT activity can be accurately determined using 18-Fluoro-Deoxy-Glucose-Positron-Emission-Tomography-Computed-Tomograpy

(18-FDG-PET-CT or PET-imaging). In our group, previous results show good determination of BAT localization and activity. In the Maastricht University Medical Centre (MUMC) there is extensive experience with VNS for epilepsy since 1999. There is a postoperative cohort of epilepsy patients of approximately 200 patients in the Kempenhaeghe institute (Heeze, the Netherlands). Fifteen patients from this cohort will be asked for two observational measurements. Both measurements will be conducted at the department of nuclear medicine of the MUMC. Before the first measurement a Dual-Energy-X-ray-Absorptiometry (DXA) scan will be made to determine body composition. Randomized by a coin toss the first measurement consists of PET-imaging with the VNS on or off. The second measurement will be similar, but on another day to allow the effect of VNS to fade out.

Addendum of mild cold exposure (version 5 of study protocol, September 2011): To compare the effects of VNS on BAT with our previous studies that assessed the effect of mild cold exposure on BAT, we will also measure the effects of VNS on BAT under mild cold conditions. We will measure 5 subjects with active VNS in both mild cold and thermoneutral conditions.

Intervention

In this study the VNS-system is switched off temporarily. This is not part of the regular VNS treatment. Theoretically this could influence the frequency of epileptic insults. On the other hand VNS is switched off frequently during regular treatment during sports or public speaking. Therefore we do not expect an increased risk of epileptic insults.

Study burden and risks

The absorbed radiation dose from the FDG PET-CT scan after administration of 74 MBq of 18F-FDG is 2.8 mSv. Subjects will be scanned twice, which is considered as a low risk.

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

Subjects treated with Vagus Nerve Stimulation (VNS) for epilepsy, aged 18-65 years, with a Body Mass Index (BMI) <= 28 kg/m2. Patients need to have optimally adjusted, stable VNS as judged by the treating neurologist.

Exclusion criteria

• Body Mass Index > 28 kg/m2
• Daily epileptic insults.
• Subjects that need or needed *Rapid Cycling* VNS to control their frequency of epileptic insults.
• Psychological unstable subjects (as judged by the treating neurologist).
• subjects with mental retardation (as judged by the treating neurologist).
• subjects with severe behaviour disorders (as judged by the treating neurologist).
• Pregnant subjects.
• Subjects that previously underwent high dose radiation for diagnostic or therapeutic purposes (radiotherapy, high frequency CT-scans).
• The use of the following medication is an exclusion criterium;
o ß-blockers,
o Ketogenic diet
• Subjects that recieved high doses of ionising radiation (x-ray or gamma radiation) in their medical history will be excluded.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-04-2011
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	04-02-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-11-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-06-2012
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	NL34114.068.10
Other	www.clinicaltrials.gov, MEC 10-3-071, "Study of the effect of vagus nerve stimulation on human brown adipose tissue activity"