Magnetic resonance analyses of cooling dynamics of brown adipose tissue in healthy adults

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1. To adapt and optimize the MR protocol to enable multi-parametric dynamic acquisitions during 1 hour of mild-cold exposure.2. To investigate tissue dynamics of metabolic activity of the hypothalamus, BAT, and skeletal muscles, measured by dynamic...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON54057

Source
ToetsingOnline

Brief title
Dynamic quantitative MR in BAT

Condition

- Lipid metabolism disorders

Synonym
obesity overweight

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Brown adipose tissue (BAT), Lipid metabolism, MRI, Thermogenesis

Outcome measures

Primary outcome

The main study parameters for both objectives are dynamic MR outcomes in response to mild-cold in the hypothalamus, BAT and skeletal muscles.

Secondary outcome

Only applicable to objective 2:

- Dynamic MR outcomes in the hypothalamus, BAT and skeletal muscles during thermoneutrality (32°C)

- Cold-induced changes in serum markers for sympathetic output (norepinephrine, epinephrine)

- Cold-induced changes is serum markers for glucose metabolism (glucose, insulin, cortisol)

- Cold-induced changes in serum markers for lipid metabolism (triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), high density lipoprotein cholesterol (LDL-C), free fatty acids)

- Cold-induced changes in BAT markers(e.g. microRNA92a, FGF21, peroxidized lipids, lysoPC(16:0), lysoPC(16:1) and PC(32:1))

- Cold-induced changes in lipoproteins

Study description

Background summary

The main function of brown adipose tissue (BAT) is to convert chemical energy stored in lipids into thermal energy (heat). Therefore, BAT is considered as a promising target to combat cardiometabolic diseases. Cold exposure is the main physiological stimulus for BAT activation. Cold exposure stimulates cation channels in the skin, which stimulate afferent nerves that transfer the cold perception to the hypothalamus. Once the signal is received by the hypothalamus, it triggers two thermogenic responses in the body: non-shivering and shivering thermogenesis. Non-shivering thermogenesis is mainly produced by the activation of BAT, where the hypothalamus activates BAT via the sympathetic nervous system, and heat is generated by the combustion of free fatty acids within the mitochondrial machinery of brown adipocytes. The combustion of free fatty acids decreases the lipid content in BAT, and perfusion is increased upon activation. In shivering thermogenesis, skeletal muscle are rapidly contracting, and thereby generate heat. However, this classical distinction between non-shivering and shivering thermogenesis is under debate, as it was recently shown that also several skeletal muscles are active during non-shivering thermogenesis. It is still unclear how the physiological responses in BAT and skeletal muscle are triggered in response to cold, and how they are coordinated by the hypothalamus.

The most common method used to evaluate BAT activity in humans is fluorine-18 deoxyglucose [18F]FDG PET-CT. This technique quantifies metabolic tissue activity based on the uptake of a glucose analogue, even though it is known that the primary substrate for BAT is fatty acids. Moreover, this technique is invasive and depends on radiation. Alternatively, magnetic resonance (MR) imaging has been proposed as a non-invasive technique to quantify the metabolic activity of this tissue via water-fat quantification. As such, it targets lipids directly. MR imaging of the BAT depot in humans located in the supraclavicular fossa has shown decreases in fat fraction (FF) of this depot after cooling, indicating the sensitivity of the technique to detect physiological changes.

Another important advantage of MR is that it enables the use of multiple scans within one imaging session. This allows assessment of other parameters, such as perfusion or temperature, but also other tissues, such as skeletal muscles or the brain. While methods to assess FF in the supraclavicular fossa are relatively well established, protocols for alternative parameters (i.e., perfusion, temperature etc.), or the use of protocols to simultaneously assess multiple tissues within one cooling session, are still an active research topic.

Study objective

1. To adapt and optimize the MR protocol to enable multi-parametric dynamic acquisitions during 1 hour of mild-cold exposure.

2. To investigate tissue dynamics of metabolic activity of the hypothalamus,

BAT, and skeletal muscles, measured by dynamic MR acquisitions, in combination with blood markers during mild-cold exposure in healthy adults.

Study design

This study is an intervention study, which will be conducted at the Leiden University Medical Center (LUMC). For objective one, we have included one study visit and the duration of this study day is circa 120 minutes. For objective two, we have included three visits, a screening visit and two study visits. The duration of the screening visit is circa 30 minutes and the study visits will each take circa 120 minutes.

Intervention

Subjects will be exposed to mild-cold using a dedicated cooling device (Blanketrol® III, Cincinnati Sub-Zero (CSZ) Products, Inc). The system consists of a heater, a compressor, a circulating pump and blankets/pads. This device can be utilized for hypo-and hyperthermia applications and offers a rapid or gradual temperature management control.

One or two water-circulating blankets will be placed around the subject positioned in the MR scanner and the blankets will be connected to the Blanketrol® III system via the waveguide. The system displays the water temperature, which will be initially set to circa 32°C to maintain thermoneutral conditions, after 20 minutes at thermoneutrality we will directly set the temperature to 18°C to initiate the cooling phase. The thermal perception of subjects will be monitored using a numeric rating scale (1=comfortable and 10=extreme cold) every 15 minutes. When the subject reports shivering, we will switch off the cooling device and get the subject out of the scanner.

For objective 2, we have also included a thermoneutral control measurement. This measurement has the same set-up as the cooling experiment, but the temperature of the blankets will be kept constant at 32°C for the entire length of the measurement.

Study burden and risks

Subjects with contraindications for MR imaging will be excluded. There are no known risks associated with the use of the MR scanner. The mild cooling protocol, in which a special cooling device is used, is generally well tolerated and no side effects are expected. The occurrence of hypothermia as well as potential other disadvantageous effects are highly unlikely and also have never occurred before in previous studies (p16-023, p16-078) that have been performed at the LUMC. Subjects have no personal benefit from participating in this study. With respect to the burden of the second part of

the study (objective 2), in total 67.5 mL of blood will be drawn per subject.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

objective 1 (MR protocol optimization):
- Age between 18-45 years
- BMI 18-25 kg/m2

objective 2:
- Age between 18-35 years
- BMI 18-25 kg/m2
- White Caucasian men and women

Exclusion criteria

Diagnosed medical conditions known to affect lipid/glucose metabolism, BAT activity or cardiac function

Medication known to affect lipid/glucose metabolism, BAT activity or cardiac function (e.g. beta blockers, thyroid supplements, antidepressants)

Inability to lay still for longer than 30 minutes

Smoking

Recent excessive weight change

Contraindications to MR scanning

Any significant chronic disease resulting from the screening sample (objective 2 only)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-09-2020
Enrollment:	300
Type:	Actual

Medical products/devices used

Generic name:	Blanketrol III;3T MRI;InBody720
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	24-07-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	08-03-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	NL73361.058.20

Study results

Date completed: 26-01-2024

Actual enrolment: 38

Summary results
Trial is onging in other countries