Stimulation of the beta-2 adrenergic receptor for activating human brown adipose tissue

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1. To investigate the acute effect of ADRB2 activation, via intravenous administration of salbutamol (250 µg), on 18F-FDG uptake by BAT.2. To assess the acute effect of ADRB2 activation via intravenous administration of salbutamol (250 µg) on...

Ethical review	Approved WMO
Status	Completed
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON54946

Source
ToetsingOnline

Brief title
The beta-2 adrenergic receptor in human BAT

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- 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: Deze studie wordt gefinancierd door

persoonsgebonden beurzen van het diabetes fonds voor dr. M.R. Boon (grant 2015.81.1808).

Intervention

Keyword: Beta-2 adrenergic receptor, Brown adipose tissue, Energy metabolism, PET/CT scan

Outcome measures

Primary outcome

- Glucose uptake by BAT, as measured by dynamic 18F-FDG PET/CT acquisition

Secondary outcome

- Resting energy expenditure, as measured by indirect calorimetry

- Serum markers for lipid metabolism (triglycerides (TG), total cholesterol

(TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein

cholesterol (LDL-C), free fatty acids)

- Lipid pathway analysis using lipidomic analysis in plasma samples

- Serum markers for glucose metabolism (glucose, insulin)

- Circulating plasma BAT markers (e.g. microRNAs)

Study description

Background summary

The prevalence of obesity and associated metabolic diseases is increasing at a disturbing rate. Type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) are currently the leading cause of global death. Obesity is the result of energy intake exceeding energy expenditure. An important contributor to energy metabolism and a promising target to counterbalance the positive energy balance in obesity is brown adipose tissue (BAT). BAT is a thermogenic organ that is able to combust triglyceride-derived fatty acids and glucose into heat. Naturally, the most well-acknowledged activator of BAT is cold exposure, which provokes an increased sympathetic outflow towards beta-adrenergic receptors on BAT. In rodents, the beta-3-adrenergic receptor (ADRB3) is predominantly found on brown and white adipocytes and activation of the ADRB3 has been shown to

effectively activate BAT and improve (cardio)metabolic outcomes.
Although in humans the ADRB3 agonist mirabegron increases 18F-fluorodeoxyglucose (18F-FDG) uptake by BAT, increases whole body lipolysis and increases resting energy expenditure, this only occurs after administration of a very high dosage of 200 mg, which highly exceeds the therapeutic dose to treat hyperactive bladder via ADRB3 activation (i.e. 50 mg). Since at 200 mg also cardiovascular side effects occur, mirabegron probably cross-reacts with ADRB1 and ADRB2. Furthermore, RNA sequencing analyses on human BAT showed, in contrast to mice, a negligible ADRB3 expression with a high ADRB2 expression. In vitro studies indeed indicate that ADRB2 is responsible activation of human BAT: 1) mirabegron increases oxygen consumption by human brown adipocytes that is inhibited by a specific ADRB2 antagonist, 2) the ADRB2 agonist formoterol activates oxygen consumption by human brown adipocytes, and 3) specific knock-down of ADRB2, and not ADRB1 or ADRB3, reduces oxygen consumption by human brown adipocytes. Whether an ADRB2 agonist is able to activate human BAT in vivo has not been investigated yet, but the fact that several studies unequivocally show an increase in resting energy expenditure, lipolysis and lipid oxidation after intravenous (IV) administration of the ADRB2 agonist salbutamol is promising.
Everything considered, we hypothesize that sympathetic activation of human BAT is mainly mediated by the ADRB2 rather than the ADRB3.

Study objective

1. To investigate the acute effect of ADRB2 activation, via intravenous administration of salbutamol (250 µg), on 18F-FDG uptake by BAT.
2. To assess the acute effect of ADRB2 activation via intravenous administration of salbutamol (250 µg) on resting energy expenditure, serum markers for lipid- and glucose metabolism and plasma BAT markers.
3. To confirm that the stimulatory effect of salbutamol on 18F-FDG uptake by BAT is not mediated via the ADRB3, by showing that the acute effect of i.v. salbutamol (250 µg) on BAT is blunted by co-administration of the ADRB1/2-blocker propranolol.

Study design

The study is a randomized double-blinded cross-over trial, that will be carried out at the Leiden University Medical Center (LUMC). This trial encompasses one screening and two study days.

Intervention

For all subjects on both study days the intervention consists of intravenous (IV) injection of salbutamol. This will be combined with either placebo (day 1 or 2) or propranolol (day 1 or 2) oral capsules. In addition, to visualize supraclavicular BAT all subjects will undergo a dynamic 18F-FDG PET/CT scan on

both study days.

Study burden and risks

This study consists of three study visits: one screening visit (~1 hour) and two study days (~3.5 hours per day). A total amount of 87.5 mL blood will be drawn, divided over the three visits. In addition, on both study days participants will undergo an 18F-FDG PET/CT scan, with a radiation burden of 8.4 mSv in total. Prior to the PET/CT scan, on both study days participants will receive 250 µg salbutamol via IV injection, either in combination with placebo or with 80 mg propranolol in capsules. Several pre-cautions regarding the IV administration of salbutamol will be taken into account to prevent from severe side-effects.
Subjects will not directly benefit from participation in this study. However, the results from this study are indispensable for unravelling the working mechanism of human BAT. In addition, the results from this study could reveal new therapeutic targets to activate human BAT and could therefore contribute to the fight against the worldwide obesity epidemic. Therefore, the risks of this study are considered defensible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

White Caucasian males
Age between 18-35 years old
Lean (BMI >= 18 and <= 25 kg/m2)

Exclusion criteria

- Diabetes mellitus (determined on basis of fasting glucose levels defined by ADA criteria)
- Any other active endocrine disease (thyroid disease, any signs of Cushing*s syndrome, adrenal disease and lipid-associated disorders such as familial hypercholesterolemia)
- Any cardiac disease (i.e. ischemic cardiac disease, arrhythmias, severe heart failure)
- A first-degree family member with sudden cardiac death
- Any chronic renal or hepatic disease
- Use of beta-adrenergic receptor agonists (for e.g. asthma)
- Use of medication known to influence glucose and/or lipid metabolism or brown fat activity (e.g. beta-blockers, antidepressants, corticosteroids)
- Use of medication shown to increase risk on hypokalemia after salbutamol administration (e.g. xanthine derivatives, steroids and diuretics)
- Any other contra-indications for the use of salbutamol or propranolol
- Abuse of alcohol or other substances
- Smoking
- Participation in an intensive weight-loss program or vigorous exercise program during the last year before the start of the study
- Current participation in another research projects that may influence the current research project
- Participation in another research in which a PET-CT scan was performed within a year before the start of the current study
- Clinically relevant abnormalities in clinical chemistry or electrocardiogram (ECG) at screening (to be judged by the study physician)

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	28-06-2021
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Propranolol
Generic name:	Propranolol hydrochloride
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ventolin
Generic name:	Salbutamol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-01-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	25-02-2021

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	17-11-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
EudraCT	EUCTR2020-004059-34-NL
CCMO	NL75061.058.20

Study results

Date completed:	24-02-2022
Results posted:	12-02-2023

First publication
13-01-2023