The effect of Mirabegron on brown adipose tissue in healthy young white Caucasian and South Asian men

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The aim of the proposed study is to investigate the effect of a *3-receptor agonist on BAT activity (MRI analysis) and energy expenditure (indirect calorimetry), in South Asian as compared to white Caucasian individuals.

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

Summary

ID

NL-OMON46185

Source
ToetsingOnline

Brief title
The effect of Mirabegron on brown adipose tissue

Condition

- Lipid metabolism disorders

Synonym
dyslipidemia, Obesity

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Het onderzoek wordt gefinancieerd met behulp van beurzen en prijzen uitgekeerd aan de onderzoekers.

Intervention

Keyword: b3 receptor agonist, Brown adipose tissue, MRI, South Asians

Outcome measures

Primary outcome

Brown sadipose tissue activity as measured with the MRI scan.

Secondary outcome

Resting energy expenditure, changes in supraclaviclair skintemperature,

parameters of glucose and lipid metabolisme and sympathic activation.

Study description

Background summary

South Asians, who are very prone to develop T2D, have less brown adipose tissue. In South Asian individuals a disadvantageous metabolic profile, including abdominal obesity, dyslipidemia and insulin resistance, is highly prevalent. As a consequence, they are at higher risk for the development of type 2 diabetes (T2D) as compared to white Caucasians and develop T2D at a younger age and lower BMI. The underlying mechanism of this increased predisposition for the development of T2D in South Asians is not understood, but is likely related to their lower energy metabolism. Interestingly, using 18F-fluorodeoxyglucose (18F-FDG) PET-CT scan analysis, we have recently shown that South Asian individuals have less brown adipose tissue (BAT) than white Caucasians. BAT has recently been discovered as a major player in energy metabolism in humans. In a process known as thermogenesis, BAT takes up fatty acids (FA) and glucose from the circulation and subsequently combusts FA and glucose into heat, thereby increasing energy expenditure and improving glucose and fat metabolism. Of note, obese individuals have lower BAT activity as compared to lean individuals and the activation of BAT is thus considered as a novel therapeutic target is the treatment of obesity and T2D.
Brown adipose tissue is activated via the ß3 adrenergic receptor: a novel therapeutic strategy? BAT is strongly innervated by the sympathetic nervous system and the most potent stimulator is cold exposure, resulting in release of noradrenalin (NA) from sympathetic nerve endings, which binds to *3-adrenergic receptors on BAT thereby enhancing thermogenesis. In fact, cold acclimatisation increases BAT volume, nonshivering thermogenesis, glucose uptake by BAT, and decreases fat mass in healthy young men. Prolonged cold exposure, however, is

not the most suitable treatment option. ß3-receptor agonists can be used to mimic sympathetic innervation of BAT. Our recent studies using mice with a human-like lipoprotein profile showed that treatment with a ß3-receptor agonist decreased fat mass, improved dyslipidemia, increased insulin sensitivity and even attenuated the development of atherosclerosis. Likewise, *3-receptor agonism has recently been shown to activate BAT in healthy young men as effectively as cold exposure. Therefore, ß3-receptor agonism would be a promising treatment option to activate BAT and enhance energy expenditure, especially for South Asians.

Study objective

The aim of the proposed study is to investigate the effect of a *3-receptor agonist on BAT activity (MRI analysis) and energy expenditure (indirect calorimetry), in South Asian as compared to white Caucasian individuals.

Study design

A randomised cross-over study consisting of three different regimes. They will receive 200 mg of a *3-receptor agonist (Mirabegron), 200 mg placebo and cold exposure (based on an individualized cooling protocol) in random order. In between the different regimes there is a wash-out period. 230 minutes after the intervention (i.e., administration of the compound, the placebo or cold exposure), BAT activity will be measured using MRI (TG content). Effects on resting energy expenditure (REE) will be monitored via indirect calorimetry with a ventilated hood system. Furthermore, plasma glucose, lipid and catecholamine concentrations will be monitored.

Intervention

Occassion 1: Mild cold exposure for a duration of 2 hours.
Occassion 2 and 3: Administration of one dose of Mirabegron (200 mg) and one dose of placebo in random order.

Study burden and risks

There is a risk of getting a heamatoma on after placing the intravenous cannula. The most reported side effects of Mirabegron are increased heart rate and nausea. During the first 3 hours after administation of the compound we will frequently monitor heartrate and blood pressure using the finapres nova.

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

* Male volunteers. 10 white Caucasians, born in the Netherlands. 10 South Asians, living in the Netherlands.
* Age: 18-30 years
* BMI * 25 kg/m2;For the patients the inclusion criteria are:
- Male or female
- Age: 20-50 years
- BMI 18-40 kg/m2
- Hetro- of homozygote mutation in LPL or high density lipoprotein-binding protein 1 (HDL-binding protein 1))

Exclusion criteria

* BMI > 25 kg/m2
* Recent excessive weight loss or exercise
* Alcohol and/ or drugs abuse

* Excessive smoking (>10 cigarettes/dag)
* Any significant chronic disease, including diabetes, Renal, hepatic or endocrine disease
* Heart disease or arrhythmias
* Thyroid disease or thyroid medication
* Hypertension
* Use of medication known to influence glucose and/or lipid metabolism or BAT activity (e.g. beta blockers or calcium channel blockers)
* Use of drugs that influence cardiac function or affect QT time
* Use of MAO inhibitor
* Use of systemic corticosteroids in previous six weeks
* Recent participation in other research projects (within the last 3 months), participation in 2 or more projects in one year
* Contraindications for undergoing an MRI scan.;For the patients the exclusion criteria are:
* Recent participation in other research projects (within the last 3 months), participation in 2 or more projects in one year
* Contraindications for undergoing an MRI scan.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-06-2016
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Betmiga

Generic name:	Mirabegron
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-02-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-04-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-07-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-11-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	30-03-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-04-2017
Application type:	Amendment
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
EudraCT	EUCTR2016-000237-48-NL
CCMO	NL56521.058.16