Targeting the beta-2 adrenergic pathway to improve skeletal muscle glucose uptake in healthy humans

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To determine if short-term treatment with the selective beta-2-adrenergic agonist clenbuterol improves glucose disposal via the mTORC2 pathway in lean, healthy male individuals with normal physical activity

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

Summary

ID

NL-OMON50072

Source
ToetsingOnline

Brief title
Human Beta-2 Adrenergic Stimulation and Muscle Glucose Uptake

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, type 2 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: ZonMw en Diabetes Fonds

Intervention

Keyword: Beta-2 adrenergic agonist, glucose homeostasis, human, skeletal muscle

Outcome measures

Primary outcome

Primary outcome parameter:

- Insulin-stimulated peripheral glucose disposal (Rd) during the high-insulin

infusion of the two-step hyperinsulinemic-euglycemic clamp

Secondary outcome

Secondary study parameters:

- Skeletal muscle GLUT4 translocation

Explorative objectives:

- Body weight/composition

- Plasma substrates

- Heart rate and blood pressure

- Insulin-mediated suppression of hepatic glucose production

- (Sleeping) energy expenditure and substrate oxidation

- Skeletal muscle glycogen and lipid content

- Gene and protein expression in skeletal muscle

- Femoral artery flow mediated dilation (FMD)

Study description

Background summary

Type 2 diabetes mellitus (T2DM) and its associated cardiovascular comorbidities have developed into a leading cause of death in western countries. Medical and non-medical treatments have failed to counter this *diabesity* epidemic, fostering the need for novel therapies. In this context, we have recently demonstrated robust improvements in insulin sensitivity in T2DM patients upon 10 days of mild cold acclimatisation, which proved to be primarily mediated through an increased skeletal muscle glucose uptake and occurred independent of improvements in classical regulatory pathways (i.e. insulin signalling or AMPK activation). Given this background, it was recently shown that skeletal muscle glucose uptake can be mediated through a novel pathway involving *2-adrenergic receptors, through activation of mTORC2. As cold-exposure is well-known to activate the sympathetic nervous system, this mechanism hence provides a likely candidate to explain effects of cold acclimatisation on skeletal muscle glucose disposal. Therefore, activation of this novel pathway could potentially be used as a novel treatment to improve skeletal muscle glucose uptake in T2DM patients. Indeed, we have recently observed dramatic improvements in glucose homeostasis in diabetic rodents upon prolonged treatment with a low-dose of the selective beta-2-agonist clenbuterol. Based on our data, activation of the beta-2-mTORC2 pathway through supplementation with a selective beta-2-agonist could significantly improve glucose tolerance in T2DM patients, thereby contributing to a positive disease outcome. However, whether the beta-2-mTORC2 pathway can be activated in humans in vivo to improve glucose disposal and thereby the glucose homeostasis, has thus far not been investigated.

Study objective

To determine if short-term treatment with the selective beta-2-adrenergic agonist clenbuterol improves glucose disposal via the mTORC2 pathway in lean, healthy male individuals with normal physical activity

Study design

This study is a randomized, placebo-controlled, double-blinded, cross-over study in which subjects will receive either the selective beta-2- agonist clenbuterol (40 microg/day) or placebo supplementation for 2 weeks with a 4-week wash-out period.

Intervention

For this study, subjects will consume clenbuterol (20 microgram/capsule) or placebo tablets twice daily (40 microgram/day) for a total period of 4 weeks (2x 2 weeks).

Study burden and risks

Participation in this study will not result in any health benefits for

subjects. This study will, however, expand our current knowledge regarding the role of the beta-2 adrenergic receptor in skeletal muscle glucose uptake and the glucose homeostasis in general. Furthermore, this study could potentially open fundamentally new therapeutic avenues to prevent and treat T2DM.

Participation to this study will pose an intermediate risk to subject's health. The main burdens for the subjects are:
- Burden of time: during this study, subjects will visit the University of Maastricht at 6 different occasions (excl. screening and incl. 2 overnight stays) in a period of 2 months. The total time which will be spend to the study is approximately 67 hours, which is excluding travelling time.
- Potential side effects of clenbuterol: Despite the fact that clenbuterol is supplemented at a low-dose, potential adverse effects could emerge, including an increased heart rate/blood pressure, tremors, muscle spasms, dizziness and headache.
- Invasive sample collection: During this study, several invasive sample collections will be performed, including blood sample collection, muscle biopsies and the hyperinsulinemic-eugluycemic clamp. These measurements could be associated with local hematoma or bruise development. However, due to the state-of-the-art techniques, risks for infection or prolonged bleeding will be minimized.
- Unexpected medical findings: During the screening and measurements of the study, unexpected medical findings might be found. Subjects will always be informed regarding unexpected findings and this information will also be communicated to the general physician.

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

1. Caucasian;
2. Male sex;
3. Age: 18-30 years
4. BMI: 20-25 kg/m2;
5. Normal physical activity levels;

Exclusion criteria

1. Not meeting all inclusion criteria
2. Cardiovascular disease (determined by means of questionnaires, heart rate/blood pressure measurements and an ECG);
3. Respiratory diseases (including asthma, bronchitis and COPD);
4. Unstable body weight (weight gain or loss > 5 kg in the last three months);
5. Intention to lose or gain body weight (e.g. with caloric restriction or physical activity)
6. Excessive alcohol and/or drug abuse;
7. Hypokalaemia;
8. Anaemia;
9. Epilepsy;
10. Smoking;
11. Renal and/or liver insufficiency;
12. Participation in another biomedical study within 1 month before the first study visit, possibly interfering with the study results;
13. Medication use known to hamper subject*s safety during the study procedures; *
14. Subjects who do not want to be informed about unexpected medical findings; *
15. Subjects who do not want that their treating physician to be informed;

16. Inability to participate and/or complete the required measurements;
17. Participation in organised or structured physical exercise;
18. Any condition, disease or abnormal laboratory test result that, in the opinion of the Investigator, would interfere with the study outcome, affect trial participation or put the subject at undue risk;
19. Hyperthyroidism

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-06-2019
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Spiropent
Generic name:	Clenbuterol hydrochloride

Ethics review

Approved WMO

Date:	09-01-2019

Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-04-2019
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-08-2019
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
EudraCT	EUCTR2018-004245-16-NL
ClinicalTrials.gov	NCT03800290
CCMO	NL67646.068.18