Is the Awakening Brain a Novel Therapeutic Target in the Treatment of Diabetes Mellitus type 2?

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON49251

Source
ToetsingOnline

Brief title
Awakening trial

Condition

- Diabetic complications
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, Insulin resistance

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC, locatie AMC
Source(s) of monetary or material Support: Diabetesfonds

Intervention

Keyword: Circadian rhythm, Dopamine, Insulin sensitivity, Type 2 Diabetes Mellitus

Outcome measures

Primary outcome

The effect of the bromocriptine intervention on i. dexamphetamine-stimulated dopamine release (SPECT imaging; * D2/3R BPND), and ii. insulin sensitivity of adipose tissue, liver and skeletal muscle (hyperinsulinemic, euglycemic clamp; percentage of insulin-induced suppression of free fatty acids (FFA) and endogenous glucose production (EGP), and insulin-stimulated rate of disappearance, respectively). Furthermore, we aim to assess the correlation between bromocriptine-induced changes in stimulated dopamine release and changes in insulin sensitivity.

Secondary outcome

The following secondary parameters will be assessed in all subjects before and after the bromocriptine intervention:

- Neuropsychological functioning and feeding behaviour characteristics assessed by questionnaires and tasks

- Dexamphetamine-induced changes in feelings of appetite and satiety measured with VAS scores, the G-FCQ-S questionnaire and a test meal (quantity of food consumed)

- Resting energy expenditure

- Body composition

Study description

Background summary

Insulin resistance and *b-cell failure are the hallmark of T2DM. While compensating for *b-cell failure with insulin treatment is effective in reducing hyperglycemia and haemoglobin A1C (HbA1C), it has serious side effects (i.e. hypoglycaemia, body weight gain) and poses a burden for the patient. Reducing insulin resistance in diabetes patients would be another logical target, but most treatment modalities have either no or modest effect on insulin sensitivity. Moreover, the lack of detailed knowledge on the pathophysiology of insulin resistance in humans is hampering the development of novel therapies. For many years, diabetes research has focussed on peripheral determinants of insulin sensitivity and although these often ground-breaking discoveries in animals led to useful novel insights in insulin signalling, translation to clinical treatment is still scarce. The brain as master regulator of energy metabolism has long been ignored in clinical diabetes research. It has been shown however that dopaminergic signalling is disturbed in obesity and we have recently shown that stimulation of striatal dopaminergic signalling improves insulin sensitivity. We here aim to follow the physiology of daily rhythmic dopamine release in reducing insulin resistance in T2DM. Furthermore we will explore the potential of bromocriptine, a dopamine agonist, as a therapeutic option for T2DM.

Study objective

With this proof-of-concept study, we will address i. differences in dopamine release in T2DM patients versus historical lean controls, ii. whether timed restoring of dopamine signalling improves dopamine release and iii. whether this reinstatement of daily dopamine rhythms is associated with an improvement in insulin sensitivity. We hypothesize that in patients with T2DM i. dopamine release is reduced in comparison to a cohort of matched historical healthy and lean controls, ii. restoring the peak in morning dopamine signalling will partially restore dopamine release, and iii. this increase in dopamine release is associated with an increase in insulin sensitivity.

Study design

A single-arm intervention study.

Intervention

Bromocriptine (DA D2 receptor agonist) orally once daily (<2 hours of awakening) during 12 weeks (in 4 weeks the dose will be build-up to 5 mg 1dd,

which is then continued for another 8 weeks).

Study burden and risks

- Bromocriptine is a dopamine receptor agonist, that has been safely prescribed for the treatment of Parkinson*s disease, hyperprolactinemia and galactorrhea for many years. As discussed above, the most common side-effects of bromocriptine are headache, sleepiness, dizziness, nausea, obstipation and vomiting (*1:100, *1:10) [SmPC]. Side effects of hypotension, allergic reaction of the skin, dry mouth, leg muscle cramps and fatigue are less frequently reported (*1:1000, *1:100). Adverse events occur more frequently with bromocriptine vs placebo ingestion, although this was only reported for the titration phase. After the initial titration phase, commonly occurring adverse events were reported at a frequency similar to that observed in the placebo treated arm. In this trial participants will be frequently screened for side-effects during both the titration and the stable phase of the bromocriptine intervention. During the titration phase, the dose of bromocriptine will only be increased when no side-effects are occurring. In addition, bromocriptine has been shown to increase insulin sensitivity, reduce the risk of cardiovascular events and to slow the progression of cardiovascular disease in T2DM patients.
- IBZM has a European (CPMP) registration, and it has been shown that it has no serious side effects. The dose equivalent per [123I]IBZM infusion amounts to 4.9 mSv (144 MBq). The total dose equivalent of the SPECT scan sessions (9.8 mSv) falls well within the maximum recommended dose equivalent for research participants (i.e. 11.3 mSv and 15.3 mSv (WHO category IIb, females and males resp., >50 years). Subjects will be provided with potassium iodide tablets on the day before, and morning of the SPECT scans, in order to reduce iodide uptake of the radioligand. Moreover, subjects are advised not to participate in research using radiation imaging in the following year and/or when they are exposed to radiation during their regular working duties.
- A low dose of i.v. dexamphetamine (0.3 mg/kg ideal bodyweight) has frequently been administered in previous studies. It has been shown that while most subjects experience large increases in happiness, restlessness and energy, other subjects experience almost no subjective effects following 0.3 mg/kg ideal bodyweight i.v. dexamphetamine, and that the quality and intensity of the subjective responses to low dose amphetamine were similar during a second exposure. Therefore, we can conclude that a low dose of 0.3 mg/kg ideal bodyweight i.v. d-amphetamine, as will be administered in the present study, will be well tolerated by the study participants. The subjective response to a single dose of dexamphetamine includes an increase in feelings of: happiness, energy, and a reduction in feelings of anxiety, and to a lesser extent some restlessness.
To monitor potential somatic side effects, such as hypertension, palpitations, tachycardia, cardiac arrhythmias and coronary spasms, subjects will be under constant vital and ECG monitoring during and after the dexamphetamine administration, in the presence of an experienced physician. Dexamphetamine

will be administered in the presence of a physician trained in resuscitation. A twelve lead ECG, a code cart and defibrillator will be available. If the systolic BP reaches or exceeds 200 mmHg for more than 5 minutes, nitroglycerine will be administered sublingually to control the blood pressure and the cardiologist on call will be notified. All subjects will be screened for the presence of cardiovascular disease by interview, physical examination, ECG at rest and during an exercise stress test.
- The stable isotope [6,6-2H2]glucose is used as a tracer, and has no radioactive properties. It behaves like its natural substrate and has been previously used without adverse effects when infused or ingested in tracer amounts.
- During the hyperinsulinemic clamp there is a risk for hypoglycaemia. This is minimised by close monitoring of plasma glucose levels, every 5-10 minutes.
- Venous blood draws can be an unpleasant experience for the participants. A low risk of phlebitis at the needle site exists; this is unpleasant, however, unharmful, of temporary nature, and self-limiting.

Worldwide, the prevalence of diabetes mellitus has quadrupled in the past thirty years, and nowadays diabetes mellitus is the ninth major cause of death. About 1 in 11 adults globally now have diabetes mellitus, 90% of whom have T2DM. Most patients with T2DM have at least one complication, and cardiovascular complications are the leading cause of morbidity and mortality in these patients. Insulin resistance and *-cell failure are the hallmark of T2DM. While compensating for *-cell failure with insulin treatment is effective in reducing hyperglycemia and HbA1C, it has serious side effects (i.e. hypoglycaemia, body weight gain) and poses a burden for the patient. Reducing insulin resistance in diabetes patients would be another logical target, but most treatment modalities have either no or modest effect on insulin sensitivity. Moreover, the lack of detailed knowledge on the pathophysiology of insulin resistance in humans is hampering the development of novel therapies. Studying the central regulation of glucose metabolism by brain dopaminergic systems opens up new avenues and possibilities in the development of novel therapies. Furthermore, restoring dopaminergic signalling with the aim to reinstate normal dopamine daily rhythms and improve glucose regulation in insulin resistant patients with T2DM is an attractive hypothesis to be studied since dopamine agonists are well tolerated, safe and cheap. Finally, bromocriptine has also been associated with beneficial effects on cardiovascular outcomes and therefore may also prove useful in the prevention of T2DM-related cardiovascular diseases.
We will keep the risks associated with participation to a minimum. Given the expected results, we thus believe that the scientific value of our findings will outweigh the burden and risks associated with participation.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Overweight/obese (BMI>25.0 kg/m2) T2DM patient, treated with oral glucose lowering medication (except for DDP4-inhibitors).
- Age 50-70 years
- Males and postmenopausal females: (history, amenorrhoea, elevated FSH)
- Stable weight (<10% change in bodyweight for 3 months prior to assessments)
- Ability to provide informed consent.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- any current somatic (except for stable obesity- or T2DM-related comorbidities) or psychiatric disorder;
- shift work
- uncontrolled hypertension
- the use of excessive alcohol or recreational drugs
- smoking
- any use of medication (including NSAIDs) except for lipid lowering, blood pressure lowering drugs and occasional use of paracetamol (less frequent than 2 days a week)
- history of psychiatric disorder or drug- or alcohol abuse
- history of cerebro- and/or cardiovascular diseases
- history of the use of dexamphetamine or dopamine agonists
- abnormal ECG at rest or during the exercise stress test
- positive family history of sudden death
- childhood-onset obesity
- history of bariatric surgery
- allergy or hypersensitivity to ergot alkaloids
- allergy or hypersensitivity to sympathomimetic amines

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-05-2019
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Parlodel
Generic name:	Bromocriptine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 22542
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2018-003607-19-NL
CCMO	NL67560.018.18
Other	NL7622
OMON	NL-OMON22542

Study results

Date completed:	24-11-2021
Actual enrolment:	17

Summary results
Trial ended prematurely