Bromocriptine bij type 2 diabetes mellitus

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Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22542

Source
Nationaal Trial Register

Brief title
AWAKENING trial

Health condition

Type 2 diabetes mellitus

Sponsors and support

Primary sponsor: Amsterdam UMC, location AMC Meibergdreef 9 1105AZ Amsterdam The Netherlands
Source(s) of monetary or material Support: Het Diabetes Fonds

Intervention

Outcome measures

Primary outcome

Dexamphetamine-stimulated dopamine release and insulin sensitivity

Secondary outcome

- Correlations between striatal dopamine D2/3 Receptor binding potential (D2/3R BPND) and stimulated dopamine release with outcomes on several neuropsychological assessments of feeding behaviour, habit formation and impulsivity (questionnaires and tasks) - Correlation between stimulated striatal dopamine release and feelings of appetite and satiety (questionnaires and test meal)

Study description

Background summary

Insulin resistance and b-cell failure are the hallmark of T2DM. While compensating for □-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. 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. Study population: we intend to include 40 T2DM patients, aged 50-70 years. Intervention: Bromocriptine (Dopamine D2 receptor agonist) orally, once daily (within 2 hours after awakening) during 12 weeks (in 4 weeks the dose will be up titrated to 5 mg, which is then continued for another 8 weeks). Main study parameters/endpoints: The effect of the bromocriptine intervention on i. dexamphetamine-stimulated dopamine release (SPECT imaging; Δ 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.

Study objective

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 total of 8 visits: Visit 1 Visit 2 and 3 Visit 4 after 2 weeks Visit 5 after 4 weeks Visit 6 after 8 weeks Visit 7 after 12 weeks Visit 8 after 13 weeks

Intervention

Bromocriptine orally, once daily during 12 weeks

Contacts

Public
Amsterdam UMC, location AMC
Jamie van Son

+31205666964
Scientific
Amsterdam UMC, location AMC
Jamie van Son

+31205666964

Eligibility criteria

Inclusion criteria

- Overweight/obese (BMI>25.0 kg/m2) T2DM patient, treated with oral medication only

Exclusion criteria

- 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
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-03-2019
Enrollment:	40
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	22-03-2019

Application type: First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 49251
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL7622
CCMO	NL67560.018.18
OMON	NL-OMON49251

Study results