The effect of insulin-induced hypoglycemia on brain lactate accumulation and regional cerebral blood flow, an explorative study

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The primary objective of this study is to investigate the effect of hypoglycemia on brain lactate accumulation and regional cerebral blood perfusion in humans. The secondary objective is to assess whether this effect is a related to hypoglycemia...

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

Summary

ID

NL-OMON40939

Source
ToetsingOnline

Brief title
The effect of hypoglycemia on brain lactate accumulation and CBF

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes, Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Het Diabetes Fonds en The European Foundation for the Study of Diabetes

Intervention

Keyword: Brain lactate accumulation, cerebral blood flow, Hypoglycemia unawareness, T1DM

Outcome measures

Primary outcome

The main study parameter is the concentration of lactate in the brain.

Secondary outcome

Secondary endpoints will be:

- Level of plasma counterregulatory hormones (glucagon, adrenaline,

noradrenaline, growth hormone and cortisol) (pmol/L)

- Glucose infusion rate (GIR): the amount of glucose 20% necessary to maintain

plasma glucose at steady state euglycemic or hypoglycemic values (mg*kg-1*min-1)

- Brain perfusion, determined by arterial spin labelling (ASL) MRI, measured

twice (at stable euglycemic and hypoglycemic levels) (ml/min)

- Hypoglycemic symptoms scores

- Plasma lactate concentration (mmol/L)

Other study parameters

- Plasma glucose concentration (mmol/L)

- Plasma insulin concentration (pmol/L)

Study description

Background summary

Iatrogenic hypoglycemia is the most frequent acute complication of insulin therapy in people with type 1 diabetes. Recurrent hypoglycemic events initiate a process of habituation, characterized by suppression of hypoglycemic symptoms and lead to hypoglycemia unawareness, which in itself defines a particularly high risk of severe hypoglycemia. Recent evidence suggest a pivotal role for increased brain lactate transport capacity in the pathogenesis of hypoglycemia unawareness. However, there is uncertainty about the magnitude of this effect and whether such excess brain lactate is oxidizes as a glucose-sparing alternative energy source or acts as a metabolic regulator controlling brain glucose metabolism, oxygen consumption and cerebral blood flow.

Study objective

The primary objective of this study is to investigate the effect of hypoglycemia on brain lactate accumulation and regional cerebral blood perfusion in humans. The secondary objective is to assess whether this effect is a related to hypoglycemia unawareness or a consequence of T1DM per se.

Study design

Cross-over intervention study

Intervention

Hyperinsulinemic stepped euglycemic-hypoglycemic glucose clamps, where plasma glucose levels will be clamped at ~5.0 mmol/l for 30 minutes and subsequently at ~3.0 mmol/l for another 30 minutes, will be performed. 1H magnetic resonance spectroscopy (MRS) will be applied during the whole test to measure brain lactate levels, and arterial spin labeling (ASL) will be used to measure brain perfusion.

Study burden and risks

The hypoglycemic condition is likely to produce typical symptoms (e.g. sweating, feeling hungry, palpitations) in healthy volunteers and T1DM patients with intact hpoglycemic awareness, but is usually well-tolerated and the risk for more severe hypoglycemia is negligible. The use of venous and arterial catheters may lead to hematomas, yet this is self-limiting and has in our hands never lead to permanent damage. 1H-MRS is a non-invasive method involving high magnetic fields, which is not associated with adverse events other than possible claustrophobia due to lying in the small MR-bore.

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

Inclusion criteria for healthy subjects;
- Age: 18-50 years
- Body-Mass Index: 18-30 kg/m2
- Blood pressure: <160/90 mmHg;Inclusion criteria T1DM patients with normal hypoglycemic awareness
- Diabetes duration >= 1 year
- Age: 18-50 years
- Body-Mass Index: 18-30 kg/m2
- HbA1c: 42-75 mmol/mol (6-9%)
- Outcome Clarke questionnaire: 0-1
- Blood pressure: <160/90 mmHg;Inclusion criteria T1DM patients with hypoglycemia unawareness

- Diabetes duration >= 1 year
- Age: 18-50 years
- Body-Mass Index: 18-30 kg/m2
- HbA1c: 42-75 mmol/mol (6-9%)
- Outcome Clarke questionnaire:>3
- Blood pressure: <160/90 mmHg

Exclusion criteria

Exclusion criteria for healthy subjects;- Inability to provide informed consent;- Presence of any medical condition that might interfere with the study protocol, such as brain injuries, epilepsy, a major cardiovascular disease event or anxiety disorders;- Use of any medication, except for oral contraceptives;- MR(I) contraindications (pregnancy, severe claustrophobia, metal parts in body);Exclusion criteria for all T1DM patients;- Inability to provide informed consent;- Presence of any other medical condition that might interfere with the study protocol, such as brain injuries, epilepsy, a major cardiovascular disease event, anxiety disorders, or complications of T1DM (including neuropathy and retinopathy);- Use of any other medication than insulin, except for oral contraceptives or stable thyroxine supplementation therapy;- MR(I) contraindications (pregnancy, severe claustrophobia, metal parts in body)

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):	24-09-2014
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Novorapid
Generic name:	Insulin aspart
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-06-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-09-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-01-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2014-001777-13-NL
CCMO	NL49093.091.14
Other	nog niet bekend

Study results

Date completed:	01-06-2015
Actual enrolment:	21