GM3 and insulin sensitivity

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We hypothesize that membrane-residing gangliosides are elevated in obese insulin resistant subjects and correlate to peripheral insulin resistance. Furthermore, we hypothesize that the perturbation of the insulin signaling cascade by elevated muscle...

Ethical review	Approved WMO
Status	Pending
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON32641

Source
ToetsingOnline

Brief title
GM3 study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes, Insulin resistance

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Fonds Metabolisme;Diabetes fonds

Intervention

Keyword: gangliosiden, GM3, insulin sensitivity

Outcome measures

Primary outcome

- Peripheral insulin sensitivity

- GM3 concentration in skeletal muscle and abdominal adipose tissue

Secondary outcome

- plasma concentration of glucoregulatory hormones

- energy expenditure

- carbohydrate oxidation and fat oxidation

- VO2 max

- Muscle fiber type

Study description

Background summary

Background
Diabetes is affecting 5% of the Western population, and is becoming more and more a problem in all age categories. Although type II diabetes was at first mainly a problem of the elderly, the incidence in children and adolescents is rapidly increasing. This increment runs in parallel with the increment in the prevalence of obesity.
Obesity induces hepatic and peripheral insulin resistance. The underlying mechanism has not been elucidated completely. However it has been convincingly demonstrated that elevated free fatty acids (FFA) are one of the major players in the induction of obesity-induced insulin resistance. The increase in free fatty acids originates from ongoing lipolysis under hyperinsulinemic and basal conditions. Peripheral glucose disposal under hyperinsulinemic conditions occurs mainly in skeletal muscle (1). Therefore many studies have focused on this tissue to get more insight in the mechanisms behind the decreased glucose uptake as seen in obesity-induced peripheral insulin resistance.
Insulin binding to the insulin receptor stimulates a complex insulin signaling cascade, eventually resulting in translocation of the glucose transporter 4 (glut4) to the plasma membrane. Many ex vivo, in vitro and in vivo experiments in cell lines, animals and humans have identified possible explanations for the reduced glucose uptake in skeletal muscle. The following mechanisms have been

proposed:
1. increased reactive oxygen species (ROS) production (2;3)
2. a pro-inflammatory state of adipose tissue resulting in dysfunctional adipocytes and ongoing production of local and systemic cytokines. Inflammatory cytokines released from adipocytes or macrophages infiltrating adipose tissue may antagonize insulin action. (4)
3. mitochondrial dysfunction induced by increased intracellular levels of peroxidized fatty acids
4. Ectopic uptake of fat. Accumulation of intramyocellular lipid and its metabolites, so called lipid toxicity, leads to insulin resistance. (5)
In this study we want to focus on this latter possible mechanism for insulin resistance.
Once fatty acids enter the cell, they are activated to acyl-CoAs and follow two predominant routes, i.e. incorporation into complex lipids (triglycerides, diacylglycerol, phospholipids, cholesteryl esters) or intra-mitochondrial beta-oxidation. Increased availability of the long chain fatty acids palmitate and stearate may result in increased formation of the intracellular glycolipid ceramide. Ceramide has been shown to interfere negatively with the insulin signaling pathway(6). Higher levels of muscle ceramide have been reported in obese subjects in some but not all human studies(7). Ceramide is a precursor for gangliosides, which may also be involved in the induction of saturated fatty acid-induced insulin resistance(8). Gangliosides reside within the plasma membrane and are able to modulate insulin signaling at the level of the insulin receptor (9-13). The most abundant ganglioside is GM3 (14) Indeed GM3 synthase knockout mice have enhanced insulin sensitivity and are protected from high fat diet-induced insulin resistance(15). Recently, we and others have shown in rats that pharmacologically reducing GM2 and GM3 levels results in amelioration of high fat diet induced insulin resistance (16;17). Whether this is also true for the human situation is not known. (18)
Whether levels of muscle and adipose tissue gangliosides are elevated in obese insulin resistant subjects remains to be answered. To explore whether gangliosides are indeed elevated in obese subjects compared to matched healthy controls and whether this is correlated to peripheral insulin resistance, we propose a study with obese and lean subjects in whom, we will measure muscle and adipocyte residing gangliosides and glucose metabolism using stable isotopes.

Study objective

We hypothesize that membrane-residing gangliosides are elevated in obese insulin resistant subjects and correlate to peripheral insulin resistance. Furthermore, we hypothesize that the perturbation of the insulin signaling cascade by elevated muscle gangliosides is caused by a reduced phosphorylation of the insulin receptor.

Study design

We will perform a hyperinsulinemic euglycemic clamp using stable isotopes, in 10 obese insulin resistant subjects and in 10 healthy lean subjects, matched for age and sex. At the beginning and end of the clamp a muscle biopsy from the vastus lateralis and a fat biopsy from the abdominal subcutaneous adipose tissue will be performed.

Study burden and risks

-Stable isotopes behave as the natural substrate and have no side effects

-A possible side effect of the administration of insulin is hypoglycaemia. Since we will measure the plasma glucose every 5 minutes and the scope of the protocol is to maintain the blood glucose stable at 5 mmol/l, hypoglycaemia is not expected

-The total volume of blood sample for the entire protocol is 150 ml. This amount is not considered to be of negative influence to the subject*s health.

-During the muscle and fat biopsy, subjects should not experience any discomfort, since the biopsy area will be adequately anaesthetized. The day after the biopsy subjects may experience a soar feeling at the biopsy location, which will resolve in a few days after the biopsy. Safety measurements will be taken to reduce the risk for a haematoma (pressure bandage). In our experience, muscle biopsy is tolerated well and leaves minimal scarring.

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

- written informed consent
- Caucasian
- able to keep a normal day and night rhythm during the study period (i.e. no shift work)
- stable weight for at least 3 months
- age 20-55 years
AND Inclusion criteria for healthy volunteers:
- 20 * BMI * 25 kg/m2
- fasting glucose level of < 5.6 mmol/L, in addition to a glucose level of < 7.8 mmol/L at 2 hours after intake of 75 g glucose (OGTT).;OR Inclusion criteria for obese subjects:
- BMI >30 kg/m2
- fasting glucose level of < 7 mmol/L, in addition to a glucose level of < 11.0 mmol/L at 2 hours after intake of 75 g glucose (OGTT).
- HOMA IR > 2.7

Exclusion criteria

- participation in an investigational drug trial within 90 days prior to our study
- history of or current abuse of drugs or alcohol (>14 U/week)
- smoking
- vigorous physical activity
- family history of DM II
- familial dyslipidemia
- any medical condition except hypertension and dyslipidemia in the obese group
- use of any medication except for anti-hypertensives, excluding ACE-inhibitors/AII-antagonists

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2008
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
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

No registrations found.

In other registers

Register	ID
CCMO	NL25129.018.08