A Dose-Response Study of Human Unacylated Ghrelin on Glycemia during Oral Glucose Tolerance Test in Patients with Type 2 Diabetes Mellitus.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27562

Source
Nationaal Trial Register

Health condition

diabetes
ghrelin
insulin

Sponsors and support

Primary sponsor: none
Source(s) of monetary or material Support: None

Intervention

Outcome measures

Primary outcome

Change in glucose levels.

Secondary outcome

Change in insulin levels.

Study description

Background summary

Ghrelin is a 28 aminoacid peptide that is naturally secreted by the stomach and circulates into 2 different forms: acylated ghrelin (AG), commonly referred to ghrelin, is acylated (octanoyl moiety) on the Serine in position 3, and unacylated ghrelin (UAG), also named un-octanoylated ghrelin, devoid of the acylated moiety.

Ghrelin has been discovered in 1999 as the endogenous ligand of an orphan receptor (GHSR 1a) that had previously been identified as the receptor mediating the pharmacological effects of a new therapeutic class of compounds, the growth hormone secretagogues (GHS).
Ghrelin has been initially characterized for its property of inducing growth hormone (GH) secretion, hence its name, GH-relin, a function mediated by GHSR1a(1;3). Since unacylated ghrelin does not bind to this receptor and has no physiological effect on GH secretion, it has long been considered as a product with no physiological role. As of today, the ghrelin system is known to exhibit numerous biological effects on the secretion of several pituitary hormones, on the gastric acid secretion and motility, on
the exocrine and endocrine pancreatic function, on glucose metabolism, on appetite stimulation and on the cardio-vascular system.
Unacylated ghrelin is known to act on some of these systems, sometimes agonizing, sometimes antagonizing the effects of ghrelin. In particular, unacylated ghrelin has been shown able to prevent the hyperglycaemic effects of ghrelin, when administered concomitantly, in healthy volunteers. This initial observation was followed by several laboratory and clinical works documenting the anti-diabetogenic potential of unacylated ghrelin.
In the Erasmus MC we performed already 2 studies with UAG; one in GH deficient patients and one in morbid obese subjects without overt diabetes. Both of these studies used single bolus i.v. administrations.
Accumulated in vitro, in vivo and clinical evidence suggest that unacylated ghrelin:

1. Prevents the diabetogenic effects of acylated ghrelin: this has been evidenced in healthy volunteers(5) and in GH-deficient patients;

2. Inhibits both basal and ghrelin-induced glycogenolysis by human hepatocytes;

3. In vitro, stimulates insulin secretion from insulinoma cells and promote proliferation and inhibit apoptosis of beta cells, a very unique property;

4. Enhances portal insulin response to glucose in rats;

5. May also reduce fat deposition and triglycerides levels, as evidenced in transgenic mice overexpressing unacylated ghrelin.

Moreover, in collaboration with the University of Turin, we observed that a 16-hour continuous infusion of unacylated ghrelin in healthy volunteers increased the first-phase insulin response following meal, reduced glucose levels, and decreased FFA levels, when compared to a saline infusion. Also, preliminary data obtained by the same groups (unpublished data; study location Turin) in diet-controlled type 2 diabetes patients suggest that the continuous infusion of UAG for 5 hours reduced fasting and post-prandial glucose as well as postprandial FFA.
In addition, the proliferative and anti-apoptotic effects documented on beta cells, apparently a very unique property, support the rationale to also develop UAG in type 1 diabetes and in the pancreas islets transplantations.
Finally, results of recent experiments by the group in Turin on circulating angiogenic cells (CAC) suggest that UAG may
beneficially impact the vascular remodeling process which is known to be impaired in type 2 diabetes patients.

ABR-formulier 31332

https://toetsingonline.ccmo.nl/ccmomon.nsf/allabrs/31332-01#SectieK[21-05-2010 16:29:51].

From literature, we know that patients with so-called neuro-endocrine tumors sometimes produce large amounts of UAG, leading to serum concentrations of more than 0.1 mcg/ml). Strikingly these patients had no specific phenotype, nor complaints that suggest a direct role of UAG in these symptoms.
Moreover, we have not observed any side-effects in any of the patients that we enrolled in previous study subjects.
Taken together, our data strongly suggest that UAG might have a:

1. Broad safety range, as ultra-high serum levels don’t induce specific signs or symptoms;

2. Blood glucose lowering effect;

3. Positive effect on the first phase post-prandial insulin secretion;

4. Insulin sensitizer, potentially with insulin-sparing effect;

5. Trophic effect on the endocrine pancreas;

6. Induces weight loss by preventing fat deposition;

7. Positive effect on the lipid profile, especially on triglycerides and free fatty acids.

Study objective

Unacylated Ghrelin will improve insulin sensitivity.

Study design

No interim analyzes, final analyzes after study.

Intervention

Overnight infusion of placebo, low and high dose UAG before an oral GTT the following morning.

Contacts

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Eligibility criteria

Inclusion criteria

1. Female or Male subject of 18 years of age or older;

2. Documented diagnosis of type 2 diabetes as defined by American Diabetes Association;

3. Diagnosis of type 2 diabetes for at least 3 months prior to screening;

4. Metformin monotherapy for at least 3 months prior to screening is allowed;

5. Screening HbA1c between 6.5% and 8.5%;

6. Body Mass Index between 25 and 35 kg/m2.

Exclusion criteria

1. History of or presence of active concomitant conditions or disease that would interfere with the protocol conduct
and study assessments, as judged by the investigator;

2. History or presence of long-term type 2 diabetes complications;

3. Clinically significant abnormalities in laboratory evaluation at screening, as judged by the investigator;

4. Use of systemic corticosteroids within 60 days prior to screening;

5. If female, pregnancy or breast feeding;

6. Drug or alcohol dependence or abuse;

7. Participation in a trial of an experimental drug or device within 60 days prior to screening.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2010
Enrollment:	12
Type:	Anticipated

Ethics review

Positive opinion

Date:	30-08-2010
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 34644
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL2380
NTR-old	NTR2487
CCMO	NL31332.078.10
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON34644

Study results

Summary results
N/A