Effects of Human Unacylated Ghrelin on Insulin Sensitivity during Euglycemic-Hyperinsulinemic- Clamp in Patients with Type 2 Diabetes Mellitus

Published: 17-09-2010
Last updated: 15-05-2024

One of the he questions that remains to be answered to further elucidate the mechanism of action is whether ot not UAG improves insulin sensitivity during a euglycemis-hyperinsulinemic clampThis study aims to clarify the effects of the continuous...

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

Summary

ID

NL-OMON36378

Source
ToetsingOnline

Brief title
UAG clamp

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Obesity and mild diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Eigen middelen;maar het UAG wordt gratis verkregen dmv een unrestricted grant

Intervention

Keyword: diabetes, glucose, insulin

Outcome measures

Primary outcome

Insulin levels

Secondary outcome

Not applicable

Study description

Background summary

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:

• prevents the diabetogenic effects of acylated ghrelin: this has been evidenced in healthy volunteers(5) and in GH-deficient patients(6);
• inhibits both basal and ghrelin-induced glycogenolysis by human hepatocytes;
• in vitro, stimulates insulin secretion from insulinoma cells and promote proliferation and inhibit apoptosis of beta cells, a very unique property;
• enhances portal insulin response to glucose in rats;
• 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 post-prandial 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.

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:
• broad safety range, as ultra-high serum levels don*t induce specific signs or symptoms;
• blood glucose lowering effect;
• positive effect on the first phase post-prandial insulin secretion;
• insulin sensitizer, potentially with insulin-sparing effect;
• trophic effect on the endocrine pancreas;
• induces weight loss by preventing fat deposition;
• positive effect on the lipid profile, especially on triglycerides and free fatty acids.

Study objective

One of the he questions that remains to be answered to further elucidate the mechanism of action is whether ot not UAG improves insulin sensitivity during a euglycemis-hyperinsulinemic clamp

This study aims to clarify the effects of the continuous infusion of relative low doses of UAG on the glucose and insulin response to an oral glucose load in overweight patients with type 2 diabetes in poor metabolic control (HbA1c > 6.5%).

Study design

Single-blind, single-centre, investigator-initiated study

Intervention

Infusion of placebo or UAG during a euglycemic, hyperinsulinemic clamp

Study burden and risks

Because of the lack of side-effects in animals and human subjects during administration of UAG sofar, the risks are considered to be low

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Postbus 2040
3000 CA Rotterdam
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Postbus 2040
3000 CA Rotterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Female or Male subject of 18 years of age or older;
• Documented diagnosis of type 2 diabetes as defined by American Diabetes Association;
• Diagnosis of type 2 diabetes for at least 3 months prior to screening;
• Metformin monotherapy for at least 3 months prior to screening is allowed
• Screening HbA1c between 6.5% and 8.5%;
• Body Mass Index between 25 and 35 kg/m2;

Exclusion criteria

• 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;
• History or presence of long-term type 2 diabetes complications;
• Clinically significant abnormalities in laboratory evaluation at screening, as judged by the investigator;
• Use of systemic corticosteroids within 60 days prior to screening;
• If female, pregnancy or breast feeding;
• Drug or alcohol dependence or abuse;
• Participation in a trial of an experimental drug or device within 60 days prior to screening; 30 days for subjects that pariticpated in the oGTT study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-09-2011
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	not available
Generic name:	unacylated ghrelin

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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: 28343
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2010-019402-16-NL
CCMO	NL31349.078.10
OMON	NL-OMON28343