The effect of GLP-1 receptor activation on central reward and satiety circuits in response to food stimuli in obesity and diabetes.

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Overall objective:The overall objective is to test the hypothesis that GLP-1 receptor activation of CNS reward and satiety circuits occurs, in the context of food(-related) stimuli, and that this effect is altered in individuals with obesity and…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON36430

Source
ToetsingOnline

Brief title
Braini-Ex

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)
- Central nervous system vascular disorders

Synonym
adult onset diabetes, diabetes mellitus type 2

Health condition

obesitas

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Eli Lilly,universiteit en industrie (Eli Lilly)

Intervention

Keyword: exenatide, GLP-1, reward, satiety

Outcome measures

Primary outcome

Differences in neuronal activity in CNS reward and satiety circuits (including striatum, amygdala, orbitofrontal cortex, insula, hypothalamus), as represented by BOLD fMRI signal change from baseline (%) in response to food(-related) stimuli, between obese T2DM patients, normoglycemic obese individuals and normoglycemic healthy lean subjects.

Secondary outcome

-Differences in neuronal activity in CNS reward and satiety circuits (including striatum, amygdala, orbitofrontal cortex, insula, hypothalamus), as represented by BOLD fMRI signal change from baseline (%) in response to food(-related) stimuli, (Appendix 4) between the infusion of exenatide and the infusion of exenatide in combination with a GLP-1 receptor antagonist.

-Feeding behavior, measured as quantitative (kcal) and qualitative (energy density as well as nutrient composition; carbohydrate/fat/protein) changes in food choice during a choice-buffet lunch, will be compared between groups and conditions.

-Self-reported hunger, satiety, fullness and prospective food consumption, will

be rated on 100 mm visual analogue scales before and after the meal.

Study description

Background summary

Comparable to the role for central nervous system (CNS) reward and satiety responses in drug addiction, it has been hypothesized that excessive eating due to changes in CNS reward and satiety responses to the consummation of food is crucial in the development of obesity and type 2 diabetes (T2DM). The delivery of nutrients to the gastrointestinal tract after food ingestion activates the secretion of several gut-derived mediators, including the incretin hormone glucagon-like peptide 1 (GLP-1). GLP-1-based therapies, including GLP-1 receptor agonists such as exenatide, are currently successfully employed in the treatment of patients with T2DM. Exenatide improves glycemic control and stimulates satiety, leading to a reduction in food intake and body weight. We hypothesize that GLP-1 and exenatide affect central reward and satiety circuits and these actions may contribute to the observed GLP-1 receptor agonist-induced weight loss. It is unknown whether differences in GLP-1 receptor activation play a role in the previously observed differences between lean and obese/diabetic individuals in activity of CNS circuits involved in satiety and reward after food intake. Differences in GLP-1 receptor activation may be due to a diminished sensitivity for GLP-1 (receptor agonists) and/or, reduced GLP-1 levels in individuals with obesity and type 2 diabetes.

Study objective

Overall objective:
The overall objective is to test the hypothesis that GLP-1 receptor activation of CNS reward and satiety circuits occurs, in the context of food(-related) stimuli, and that this effect is altered in individuals with obesity and T2DM.
To this end we will address the following research objectives:

Primary Objective
1)Do the effects of the GLP-1 receptor agonist exenatide on neuronal activity of CNS reward and satiety circuits, in response to food(-related) stimuli, differ between obese T2DM patients, normoglycemic obese individuals, and normoglycemic healthy lean subjects?

Secondary Objectives

2)Are the exenatide-induced effects on the neuronal activity of CNS reward and

satiety circuits effectuated by the GLP-1 receptor agonist per se (i.e. independent of other postprandial metabolic and hormonal changes)?

3)Are the exenatide-induced effects on the neuronal activity of CNS reward and satiety circuits mediated via the GLP-1 receptor?

4)How do the GLP-1 receptor agonist-related CNS changes correlate with subsequent quantitative and qualitative aspects of food intake, including self-reported hunger, satiety, fullness, prospective food consumption, and mood, during a choice-buffet in these obese T2DM patients, normoglycemic obese individuals, and normoglycemic healthy lean subjects?

Study design

This is a randomized, single blind, cross-over mechanistic study in humans in vivo, addressing important mechanism of action of the GLP-1 receptor agonist exenatide, using a complex protocol in obese T2DM patients, normoglycemic obese individuals, and normoglycemic healthy lean subjects.

Intervention

We will investigate and compare all participants with respect to food(-related) neuronal activity in central reward and satiety circuits by blood oxygen level-dependent (BOLD) fMRI at 3 different occasions. Neuronal activity will be expressed as signal change from baseline (%) in response to food(-related) stimuli. BOLD fMRI assessment will be performed during intravenous infusion of a) the GLP-1 receptor agonist exenatide; b) the GLP-1 receptor agonist exenatide in combination with a GLP-1 receptor antagonist (exendin 9-39) or c) saline. These infusions will be performed in randomized order, on three separate days. To address the secondary objective, i.e. tease out the role of GLP-1 receptor agonist per se versus concomitant postprandial metabolic and hormonal influences on the CNS circuits, the fMRI measurements will be performed during a somatostatin pancreatic clamp with replacement of basal insulin, glucagon and growth hormone. Levels of glucose and fore-mentioned hormones will be kept at levels compatible with the postprandial state. To investigate whether the exenatide-induced effects on the CNS circuits are mediated via the GLP-1 receptor (objective 3), we will assess BOLD fMRI signal alteration of combined infusion of exenatide and a GLP-1 receptor antagonist (exendin 9-39). Finally, to correlate changes in brain activity with subsequent feeding behavior (objective 4), we will measure quantitative and qualitative food intake including self-reported hunger, satiety, fullness, prospective food consumption, and mood, during a choice-buffet immediately after the scanning period.

Study burden and risks

We are well aware of the possible demand that may be imposed on the participants in this mechanistic study. After the screening visit participants will travel 3 times to the study location. The duration of the visits is aproximately 4 hours. A total amount of 477.5 mL blood will be withdrawn in the total study (during 3 months). The risks associated with participation are the risks of venous blood drawing. Exenatide, a GLP-1 receptor agonist, will be infused according to a predefined algorithm. The only known side-effects of exenatide infusion are nausea and vomiting, however we have specifically chosen infusion rates at which the risk of the development of these undesired effects is kept to an absolute minimum. We will try to make this study as bearable as possible for our participants. All tests will be done by one researcher.

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

For all 3 study groups:
1. age 18*70 years.
2. Men and women. For women, only postmenopausal women (as ascertained by serum FSH) will be included in order to avoid variations related to the menstrual cycle.
3.To promote comparability and to overcome the interference of lateralization, only right-handed persons will be included.;For the healthy lean subjects, inclusion criteria will be:
1.body-mass index (BMI) of <25 kg/m2
2.stable bodyweight (<5% reported change during the previous 3 months)
3.Normal fasting and 2-h postload glucose as ascertained during a 75-g oral glucose tolerance test (OGTT);For the normoglycemic obese individuals, inclusion criteria will be:
1.body-mass index (BMI) *30 kg/m2
2.stable bodyweight (<5% reported change during the previous 3 months)
3.Normal fasting and 2-h postload glucose as ascertained during a 75-g oral glucose tolerance test (OGTT) ;For the obese T2DM individuals, inclusion criteria will be:
1.Diagnosed with T2DM (20) > 3 months prior to screening
2. BMI *30 kg/m2
3.HbA1c 6.5*8.5% (48-69 mmol/mol)
4.Treatment with metformin at a stable dose for at least 3 months.

Exclusion criteria

In the obese T2DM patients, no blood glucose- and weight lowering agents will be allowed within 3 months before screening except for metformin. The normoglycemic lean and obese individuals will not be allowed to take blood glucose-lowering agents at any time before and during the study.
For all individuals, exclusion criteria will be:
1.congestive heart failure (NYHA II-IV)
2.chronic renal failure (glomerular filtration rate < 60 mL/min/1.73m2 per Modification of Diet in Renal Disease (MDRD)) or serious liver impairment
3.a history of gastrointestinal disorders, including gastroparesis, pancreatitis and cholelithiasis
4.neurological illness
5.malignancy
6.pregnancy or breast feeding
7.implantable devices
8.substance abuse
9.addiction
10.contra-indication for MRI, such as claustrophobia or pacemaker
11.any psychiatric illness, including eating disorders and depression
12.hypersensitivity to the active substance or to any of the excipients
13.chronic use of glucocorticoids or centrally acting drugs within 2 weeks immediately prior to screening

14.use of cytostatic or immuno-modulatory agents
15.participation in other studies
16.individuals who have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry
17.individuals who are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
18.individuals who have previously completed or withdrawn from this study or any other study investigating GLP-1 receptor agonist or dipeptidyl peptidase (DPP)-4 within 6 months
19.individuals, who in the opinion of the investigator, are unsuitable in any other way to participate in this study
20.individuals who are employed by Amylin Pharmaceutical Inc. or Eli Lilly & company (that is, employees, temporary contract workers, or designees responsible for conducting the study). Immediate family of Amylin or Lilly employees may participate in sponsored clinical trials, but are not permitted to participate at an Amylin or Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
21.poor commandment of the Dutch language or any (mental) disorder that precludes full understanding the purpose, instruction and hence participation in the study.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-07-2011
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Byettta
Generic name:	exenatide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Exendin 9-39
Generic name:	Exendin 9-39
Product type:	Medicine
Brand name:	Genotropin
Generic name:	growth hormone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	glucagen
Generic name:	glucagon
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	somatostatin
Generic name:	somatostatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-03-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-04-2011
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
EudraCT	EUCTR2010-023635-42-NL
CCMO	NL34552.029.11