Effects of timing of food intake on glucose metabolism and the brain during a hypocaloric diet in obese subjects

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To investigate whether in obese subjects meal timing during a hypocaloric diet is related to the brain serotonergic system and insulin sensitivity as well as to food-motivated behavior.

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

Summary

ID

NL-OMON40991

Source
ToetsingOnline

Brief title
TIME-study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
type 2 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: STW subsidie (OnTime)

Intervention

Keyword: hypocaloric diet, insulin sensitivity, serotonin transporters, timing food intake

Outcome measures

Primary outcome

* Insulin sensitivity: 2-step hyperinsulinemic euglycemic clamp with stable

glucose isotope tracer

* Serotonin transporter availability : [123I]FP-CIT SPECT scan

* Serotonergic activity: pharmacological MRI using citalopram

Secondary outcome

* Motivation and impulse control: functional MRI

* Abdominal and liver fat: magnetic resonance sprectroscopy (MRS)

* Circulating hormones and substrates: blood drawing

* Sleep duration: Actiwatch

* Sympathetic and parasympathetic activity: heart rate variability

* Feeding behaviour: questionnaires

Study description

Background summary

The global occurrence of obesity has increased dramatically during the past decade. Obesity is associated with increased morbidity and mortality explained by the medical consequences of obesity, including type 2 diabetes mellitus and cardiovascular disease. Treatment of obesity is difficult and often unsuccessful because dietary restrictions frequently result in weight regain after initial weight loss probably as a result of increased motivation to eat and a rise in hunger and craving scores. The brain plays a central role in the regulation of feeding behavior, and through energy restriction multiple metabolic signals from peripheral organs will signal the brain to increase food intake and thus modulate feeding behavior in addition to weight loss induced

changes in glucose metabolism. Within the brain, serotonin is an important regulator of food intake and body weight. Extracellular serotonin concentrations, available for receptor binding and serotonin signalling, is regulated by the serotonin transporter (SERT). Interestingly, a negative association between midbrain SERT and body weight has been shown and we recently found a positive correlation between SERT and insulin sensitivity (METC nr 10/292). Moreover, we recently reported a decrease in diencephalic SERT upon a 6 weeks hypercaloric snacking diet in lean men (METC 10/247). Thus serotonin might provide a link between the changes in feeding behavior and glucose metabolism in periods of caloric excess and caloric restriction. The adaptive serotonin response to these different states might predict body weight gain or loss respectively as well the effects on glucose metabolism.
Besides the amount of consumed calories in relation to caloric need, recent studies suggest a central role for the time of the day of food intake in modulating body weight, appetite, and glucose metabolism and postulate that consuming food at inappropriate times of the day contributes to the development of obesity and insulin resistance. Importantly a recent study showed that in obese subjects during a hypocaloric diet, consuming the majority of the calories in the morning resulted in more profound and sustained weight loss in the longer term compared to consuming the majority of calories during the night. This suggests that during caloric restriction, timing of food intake is an important determinant of long term weight loss. Since timing of food intake is part of the circadian rhythm orchestrated by the brain, and serotonin is one of the signaling neurotransmitters involved in circadian rhythm, changes in the serotonergic system during hypocaloric conditions might explain these differences.
We hypothesize that during a hypocaloric diet to promote weight loss in obese subjects, consuming the majority of calories in the AM (i.e. at breakfast) results in suppression of appetite and craving and improves insulin sensitivity more compared to consuming the majority of calories in the PM (i.e. at dinner).

Study objective

To investigate whether in obese subjects meal timing during a hypocaloric diet is related to the brain serotonergic system and insulin sensitivity as well as to food-motivated behavior.

Study design

Open randomised controlled diet intervention study

Intervention

Subjects will reduce their daily caloric intake with 50% for 4 weeks. Subjects will be randomized into either a hypocaloric diet group where 15% of total kcal

have to be consumed with breakfast, 35% kcal with lunch and 50% kcal with dinner or a hypocaloric diet group where 50% of kcal have to be consumed with breakfast, 35% kcal with lunch and 15% kcal with dinner.

Study burden and risks

Total study duration is 4 weeks. Subjects will visit the AMC weekly and total visit time will be about 34 hours. At study entry, subjects will be screened for in- and exclusion criteria. Participations will follow a hypocaloric diet for four weeks after randomization. The hypocaloric diet will be based on a 50% caloric reduction which will result in a weight loss of approximately 7%. A large number of short and long term health benefits can be achieved with even 5-10% weight loss such as beneficial effects on glucose metabolism and components of the metabolic syndrome. Although dietary restriction often results in initial weight loss, weight gain after weight loss represents one of the major problems in therapeutic management of obesity. Adjusting the timing of food intake could be a useful (and practical) strategy to maintain weight loss and could have a long-term protective effect against the development of the metabolic syndrome. Before and after four weeks on the hypercaloric diet, a 2-step hyperinsulinemic euglycemic clamp will be performed using stable isotopes. Stable isotopes behave like their natural substrates and are therefore not harmful. Blood samples will be obtained from an intravenous cannula in a peripheral arm vein. Hypoglycemia during the hyperinsulinemic clamps will not occur because plasma glucose will be measured bedside at regular intervals. Total clamping time on one day will be 7 hours. Subjects will undergo a SPECT-scan with the radioligand [123I]FP-CIT, administered intravenously. At 2 and 3 hours after administration, a SPECT-scan of the brain will be performed which takes about 40 minutes each, during which the participant lies down on his back on the gamma camera bed. The day before SPECT-scan and on the morning of the scan, subjects will be given potassium iodide tablets to reduce uptake of the radioligand in the thyroid. [123I]FP-CIT has a European (CPMP) registration, and it has been shown that it has no serious side effects. As the dose equivalent per [123I]FP-CIT injection amounts to 2.4 mSv (100MBq), the total dose equivalent of the participating subjects will amount less than 10.0 mSv (222 MBq) (WHO category IIb). A pharmacological MRI will be performed following serotonin challenge with a single and low dose of the selective serotonin reuptake inhibitor (SSRI) citalopram (7.5mg intravenously) to evaluate the serotonergic system. ASL is a non-invasive cerebral blood flow imaging modality that uses magnetically labelled blood water protons as an endogenous tracer of cerebral blood flow. Citalopram is the only SSRI registered in the European Union for intravenous administration and a well-tolerated treatment for severely depressed patients and for serotonin modulation in MRI. For careful analysis of the SPECT-scan, a structural MRI of the brain will be performed. In addition an MRI of the abdomen will be performed to quantify visceral- and liver fat. The MRI-scans requires lying as quiet as possible for 75 minutes.

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

- Male
- BMI * 30kg/m2
- Age 50-80 years
- At least 3 out of 5 metabolic syndrome criteria: fasting plasma glucose * 5.6 mmol/l, triglycerides * 1.7 mmol/l, waist-circumference > 102 cm, HDL-cholesterol 1.04 mmol/l, blood pressure * 130/85 mmHg
- Stable weight three months prior to study inclusion

Exclusion criteria

- Use of any medication except for those related to treatment of components of the metabolic

syndrome (excluding insulin, oral glucose lowering drugs, beta-blockers)
- Any actual medical condition except for treated hypothyroidism and the metabolic syndrome
- History of any psychiatric disorder
- Shift work
- Irregular sleep pattern
- Intensive sports (>3/week)
- Restrained eaters
- History of eating disorders (anorexia, binge eating, bulimia)
- Smoking, XTC, amphetamine or cocaine abuse
- Alcohol abuse (>3/day)
- Contraindication MRI
- Lactose intolerance

Study design

Design

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

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-11-2014
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO

Date:	26-09-2014
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	NL49724.018.14