Effects of timing of hypercaloric snacking diets on metabolism and brain

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To determine the effects of hypercaloric HFHS snacking in the morning or evening on insulin sensitivity and serotonin function in the diencephalon.

Ethical review	Not approved
Status	Will not start
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON38544

Source
ToetsingOnline

Brief title
SNACK-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 (On Time)

Intervention

Keyword: circadian rhythm, hypercaloric diet, insulin sensitivity, serotonin transporters

Outcome measures

Primary outcome

To determine the effects of hypercaloric high-fat high-sugar snacks in the morning or evening on:

- Insulin sensitivity

- Cerebral serotonin transporter binding and 5-HT functionality

- Correlation between serotonin function and insulin sensitivity

Secondary outcome

To determine the effects of hypercaloric high fat-high high-sugar snacks in the morning or evening on:

- Accumulation of hepatic and visceral fat mass

- Free fatty acid (FFA) and triglyceride levels

- Appetite hormones: gutpeptides and leptin

- Sleep duration

- Resting energy expenditure

- Sympathetic and parasympathetic balance: heart rate variability, skin temperature

- Motivation and impulse control (functional MRI)

- Neuropsychological functioning: craving, hunger feeling and impulsivity (questionnaires)

- Hypothalamic pituitary adrenal (HPA) axis: cortisol

Study description

Background summary

Food intake has dramatically changed in the last decades and hypercaloric diets, sugar-sweetened beverages and snacking behaviour have all been associated with an increase of body weight and diabetes. Specific brain regions, including the hypothalamus and reward areas, strongly regulate feeding behaviour. Besides these regions, the circadian clock, located in the nucleus suprachiasmaticus (SCN) are involved in the regulation of food intake, glucose and fat metabolism in rodents and humans. The timing of food intake is an important external synchronizer and alterations in feeding behaviour, such as skipping breakfast, irregular meal pattern and snacking, may lead to disturbances of the circadian rhythm of metabolism and thereby contribute to obesity and insulin resistance. Cerebral serotonin is involved in food intake and regulation of body weight. Extracellular serotonin concentration, available for receptor binding and serotonin signalling, is regulated by the serotonin transporter (SERT). Serotonergic transmission and SCN physiology are strongly intertwined. SERT shows a diurnal rhythm in mice with higher expression and activity during the dark (active) phase. Moreover key signaling molecules from the serotonin signaling network, such as SERT and different serotonin receptors such as the 5-HT1B, 5-HT7, and 5-HT2C receptors are expressed in the SCN biological clock nucleus. Interestingly, we and others recently found a negative association with diencephalic SERT and body weight and a positive correlation between SERT and insulin sensitivity . Moreover, we recently found a decrease in diencephalic SERT upon a 6 weeks high fat high sugar (HFHS) snacking diet in lean men.
We therefore hypothesize that a hypercaloric HFHS snacking diet through manipulation of midbrain serotonin signalling influences metabolic rhythmicity in the SCN, which contributes to a reduction in insulin sensitivity in humans. Furthermore, shifting the snacking to inappropriate time points, i.e. during the dark phase, will more profoundly affect metabolism due to more severe misalignment.

Study objective

To determine the effects of hypercaloric HFHS snacking in the morning or evening on insulin sensitivity and serotonin function in the diencephalon.

Study design

Open randomised controlled intervention study

Intervention

Subjects will consume a 60% surplus hypercaloric diet composed of a self-selected, eucaloric healthy ad libitum diet plus a HFHS drink five times a day either before 11:30 (group 1) or after 19:30 (group 2). After the

intervention of 4 weeks, subjects will follow a hypocaloric diet to lose the gained weight.

Study burden and risks

Total study duration is 8 weeks. Subjects will visit the AMC weekly and total visit time will be about 30 hours. At study entry, subjects will be screened for in- and exclusion criteria. Participations will follow a hypercaloric HFHS diet for four weeks after randomization. The hypercaloric diet will be based on a 60% caloric surplus on top of their ad libitum diet which will result in a modest weight gain. After the hypercaloric phase, a hypocaloric diet will follow to lose the gained weight under strict supervision. Temporary weight gain does not provoke serious health risks.
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 2.7 mSv (111MBq), 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 23-27 kg/m2
- Age 18-55 year
- Stable weight 3 monthes prior to study inclusion

Exclusion criteria

- First degree with DM
- Use of any medication
- Any medical condition
- History of psychiatric disorder
- Shift work
- Irregular sleep pattern
- Intensive sport (>3 week)

- Restrained eaters
- History of eating disorders
- Lactose intolerance
- Smoking, XTC, apmphetamine or cocaine abuse
- Alcohol abuse (>3/day)
- Contraindication MRI

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:	Will not start
Enrollment:	25
Type:	Anticipated

Ethics review

Not approved

Date:	25-02-2014
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	NL46108.018.13