Dysregulation of brain reward systems in obesity: measuring endogenous dopamine levels by acute dopamine depletion

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Ethical review	Approved WMO
Status	Pending
Health condition type	Appetite and general nutritional disorders
Study type	Observational invasive

Summary

ID

NL-OMON34239

Source
ToetsingOnline

Brief title
Endogenous dopamine levels in the brain in obesity

Condition

- Appetite and general nutritional disorders

Synonym
fatty degeneration, obesity

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: brain reward system, craving, dopamine, obesity

Outcome measures

Primary outcome

- Availability of dopamine D2 receptors (D2R) in the striatum before and after

dopamine depletion (difference is baseline dopamine level)

- eating behavior

- correlations between baseline dopamine level, striatal D2R availability,

eating behavior, and BMI

Secondary outcome

Plasma and urine measurements on dopaminergic parameters

Study description

Background summary

Obesity (BMI >= 30 kg/m2) is a growing problem in the Netherlands because of its morbidity and rising prevalence. One of the most important factors in the pathophysiology of obesity is overeating of high-caloric foods.

Overeating shares similarities with addiction: compulsive behavior, loss of control of intake, and craving. In this context, it has been suggested that food and drugs of abuse may activate the same brain reward systems. The mesolimbic dopaminergic projection from the ventral tegmental area (VTA) to the ventral striatum is most frequently implicated in reward function although other forebrain dopamine projections and other brain structures are certainly involved as well. There is a large body of evidence to suggest that dopamine is one of the neurotransmitters linking factors that contribute to overeating. Several types of food induce dopamine release in a part of the ventral striatum (nucleus accumbens) in rodents. In humans, it has also been demonstrated that eating a meal induces a dopamine release in the striatum . It has been postulated that the ability of drugs of abuse and food to increase dopamine is

crucial for their reinforcing effects.

Several models have been developed to conceptualize the biochemical and psychometric changes observed in addiction. Koob and Le Moal proposed a model for brain changes that occur during the development of addiction. The proposed allostasis model is based primarily on findings from animal research. Evidence is growing, however, that a state of allostasis may exist in human addiction and possibly obesity. An important element of the model is a hypoactivated mesolimbic reward system. Several human studies found confirmation for this concept in addiction by demonstrating reduced expression of the striatal dopamine-D2 receptor (D2R). Similarly, decreased striatal D2R availability has been demonstrated in obese subjects. The expression of the striatal D2R plays an important role in motivational aspects of drug use, as it might do for food intake.

In addiction research, confirmation for the hypoactivated mesolimbic reward system has also been found by demonstrating decreased baseline dopamine levels in cocaine addicts and a blunted dopamine release on amphetamine. Whether these changes in the dopamine system are also the case in obesity has not been demonstrated yet. In this study, we want to test whether baseline dopamine levels are decreased in obesity by imaging striatal D2Rs before and after dopamine depletion. Additionally, we will test whether these levels are linked to craving for food.

Study objective

The primary goal of the proposed study is to investigate striatal D2R levels and eating behavior before and after dopamine depletion in order to build knowledge on the interactions between the brain reward system and overeating behaviour.
This will be done to gain more insight in the aetiology of obesity.

Study design

In 15 female obese subjects and 15 age matched female control subjects, the availability of D2R in the striatum will be measured with a 123I-IBZM SPECT scan before and after dopamine depletion. For these scans the subjects will visit the AMC twice within 2 weeks. Dopamine depletion will be achieved by administering AMPT, which temporarily block dopamine production, to the subjects 24 hours before the second scan. Eating behavior will be measured at the first visit with questionnaires, neuropsychological computer tasks and an interview.

Intervention

- dopamine depletion by 2-day AMPT administration

- gastric banding procedure (only for obese subjects)

Study burden and risks

The burden for the subjects consists of exposure to each of the following: 2x visit in fasten state to the AMC, 2x IBZM SPECT scan, 1x MRI scan, 1x 2-day treatment with AMPT, 2x venapunction and urine sample, 2x completing questionnaires, 1x neuropsychological computer tasks and interview.
The risks for both obese and control subjects are: radiation (within the WHO criteria for research in humans) and possible side effects of AMPT.

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

* Female;
* Age 18-45 years;
* BMI >35 of 18-25 kg/m2;
* Caucasian;
* Able to provide written informed consent and to comply with all study procedures.

Exclusion criteria

* Currently dependent on any substance including nicotine or cannabis;
* Diabetes mellitus and/or dyslipidemia;
* Hypertension necessitating more than one type of medication;
* Severe neurological or psychiatric disorders (e.g., depression, psychosis, bipolar illness, dementia, or any diseases that require psychotropic medications);
* Serious medical illnesses;
* Drugs known to influence binding to D2R, including neuroleptics, and methylphenidate;
* Clinically significant abnormal laboratory values;
* Any disease of the gastrointestinal system, liver, or kidneys which could result in altered metabolism or excretion of the study medication;
* Pregnancy or breastfeeding;
* Contraindications for MRI scan (claustrofobia, inclusion of metal components in the body, e.g. pacemaker)
* Measurements crossing maximum weight and size criteria for MRI and SPECT scanner.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2010
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO
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	NL32182.018.10