ISRCTN17965026 https://doi.org/10.1186/ISRCTN17965026

Dopaminergic neurotransmission in dietary learning and obesity

Submission date
11/07/2023

Recruitment status
No longer recruiting

Registration date
13/07/2023

Overall study status
Completed

Last Edited
19/12/2024

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Sensitivity to food rewards has received increasing interest as a determinant of obesity. Preclinical studies support that the reinforcing value of food is determined not only by its pleasant taste but also by its nutritional value, a phenomenon mediated by dopaminergic activity. However, studies of altered reward sensitivity, including taste perception, resulted in inconsistent results in human obesity, and the postingestive reinforcement was, to our knowledge, unexplored in this disorder. Thus, this project aims to study postingestive reinforcement in obesity and after bariatric surgery.

Who can participate?
Participants in an obesity management center in which surgical alternatives are offered for the treatment of obesity. Participants may also be chosen, despite not being overweight and/or being included in any weight loss consultation, to obtain data from healthy volunteers.

What does the study involve?
Participants will be invited to answer questions related to demographic characteristics, health information and habits as well as assessment of weight and height. If no factors are found in this questionnaire that prevents the individual from participating in the study, volunteers will be asked to collaborate on a six-day paradigm that involves consuming dairy-based beverages and to answer questions related to the sensations induced by this consumption. To perform these sessions volunteers will be asked to undergo an overnight fasting and to abstain from drinking any drinks except for water and from smoking. On one of the six days, volunteers will be invited to enrol in a brain imaging test, single-photon emission computerized tomography (SPECT) performed in the Nuclear Medicine – Radiopharmacology department at the Champalimaud Research and Clinical Centre. This test involves the intravenous administration of a substance with low radiation levels and a brain scan to study the binding of this substance to brain regions of interest.
An electrogustometric procedure will be carried out to measure individual taste detection threshold, as well as another test in which participants will be asked to taste several substances absorbed in filter papers. Then, participants will be asked to answer some questions about the

sensations caused by each of these substances. Once these taste assessment procedures are finished, the team will carry out a psychometric assessment using self-report reward-related measures, questionnaires about mood, feeding behavior traits and food acceptance.

What are the possible benefits and risks of participating?
This study does not imply receiving a particular medication or treatment for a disease. There are no immediate benefits from participating in this study. However, through the participation of our patients, they will be contributing to the development of scientific knowledge in this area. It is also possible that, in the longer term, the results of this study contribute to an improvement in the care provided to patients with obesity or eating disorders. The general inconveniences related to the participation result from traveling to the place where the test sessions take place and the time spent in those sessions.

Where is the study run from?
This study will be conducted by the Neuropsychiatry Unit at the Champalimaud Research and Clinical Centre, Lisbon, Portugal, and the imaging studies will be conducted by the Nuclear Medicine – Radiopharmacology department at the Champalimaud Research and Clinical Centre. The cohort will include consecutive patients with obesity at Hospital de Ehas Moniz, Centro Hospitalar de Lisboa Central E.P.E. Lisbon, Portugal.

When is the study starting and how long is it expected to run for?
June 2012 to July 2023

Who is funding the study?
The study is supported by grants from:
1. Portuguese Foundation for Science and Technology (Fundação para a Ciência e Tecnologia – FCT; PTDC/MED-NEU/31331/2017)
2. A Starting Grant from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 950357)
3. Champalimaud Foundation supported this project through a clinical fellowship (Clinical Kickstarter/RibeiroDR2Binding/2018)

Who is the main contact?
Prof Albino J. Oliveira-Maia (Director of the Neuropsychiatry Unit at the Champalimaud Research & Clinical Centre), albino.maia@neuro.fchampalimaud.org (Portugal)

Contact information

Type(s)
Principal investigator

Contact name
Prof Albino Jorge Oliveira-Maia

ORCID ID
https://orcid.org/0000-0001-5071-3007

Contact details
Director of Neuropsychiatry
Champalimaud Foundation
Av. de Brasília

Doca de Pedrouços
Lisbon
Portugal
1400-038
+351 21 048 0000
albino.maia@neuro.fchampalimaud.org

Type(s)
Scientific

Contact name
Prof Albino Jorge Oliveira-Maia

Contact details
Director of Neuropsychiatry
Champalimaud Foundation
Av. de Brasília
Doca de Pedrouços
Lisbon
Portugal
1400-038
+351 21 048 0000
albino.maia@neuro.fchampalimaud.org

Type(s)
Public

Contact name
Prof Albino Jorge Oliveira-Maia

Contact details
Director of Neuropsychiatry
Champalimaud Foundation
Av. de Brasília
Doca de Pedrouços
Lisbon
Portugal
1400-038
+351 21 048 0000
albino.maia@neuro.fchampalimaud.org

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
HMSP/ICJ/0020/2011

Study information

Scientific Title
Postingestive reinforcement in obesity and bariatric surgery.

Study objectives
In this study, it is hypothesised that postingestive reinforcement, as measured in a behavioural paradigm is impaired in obesity. Postingestive conditioning strength, measured using a previously optimised protocol controlling for orosensory cues, is compared between patients with obesity either prior to or after bariatric surgery, and healthy volunteers. All participants are also assessed with [123I] IBZM SPECT to explore potential associations with dopamine D2-like receptor (DD2lR) availability. Additional aims include testing the differential impact of gastric surgery type, i.e., gastric bypass and sleeve gastrectomy, on postingestive reinforcement as well as DD2lR availability.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 22/07/2013, Comissão de Ética da Fundação Champalimaud (Fundação Champalimaud, Avenida Brasília, Lisboa, 1400-038, Portugal; +351 210 480 200; info@fundacaochampalimaud.pt), ref: None available

2. approved 09/03/2015, Comissão de Ética para a Saúde do Centro Hospitalar de Lisboa Ocidental (Hospital de Egas Moniz. Rua da Junqueira, 126, Lisbon, 1349-019, Portugal; +351 210 432 665; chlo@chlo.min-saude.pt), ref: None available

3. approved 30/05/2016, Comissão de Ética do Centro Académico de Medicina de Lisboa (CHLN /FMUL/IMM) (Avenida Professor Egas Moniz, Lisbon, 1649 - 035, Portugal; +351 217 548 000; ana. pimentel@chln.min-saude.pt), ref: 124/16

Study design
Cross-sectional observational study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Obesity

Interventions
This cross-sectional observational study will compare patients with obesity either before or after bariatric surgery (gastric bypass or sleeve gastrectomy) and a group of healthy controls. Data will be collected using flavour-nutrient conditioning (FNC) previously optimised and validated in a distinct cohort of over 200 healthy individuals. FNC consists of the induction of a conditioned preference for a flavour delivered orally, resulting from repeated pairings with the postingestive consequences of a nutrient. Here, FNC is conducted with sweetened low-fat yogurt solutions, with either maltodextrin (unconditioned stimulus) or carboxymethylcellulose (control stimulus), paired with two distinct flavours (respectively CS+ and CS-). Home-conditioning is performed

with 2 days of CS+/Maltodextrin, alternated with 2 days of CS-/CMC. Preference for CS+ is assessed in the laboratory immediately prior to and after conditioning.

Participants will also be evaluated using nuclear medicine imaging of striatal dopamine D2-like receptors (DD2lR availability), Single Photon Emission Computerised Tomography (SPECT) with [123I]-Iodobenzamide ([123I]IBZM.

The clinical sample consists of consecutive patients at a tertiary care outpatient center specialised in the surgical treatment of obesity, belonging to Centro Hospitalar de Lisboa Ocidental, E.P.E., in Lisbon, Portugal.

The sample includes a group of patients on the waiting list for bariatric surgery (obese group) and a group of patients that had received bariatric surgery (surgical group). The latter is recruited 1.5 to 4 years after either gastric bypass or sleeve gastrectomy when patients are expected to be weight stable and capable of consuming small volumes of liquid. Approval for bariatric surgery follows standard criteria as defined by the Portuguese National Health Service.

The clinical team identifies patients, and those consenting to be contacted are screened by phone call. Those that are not excluded are further assessed for eligibility at admission into the study. For patients, we retrieve the surgery date and type (i.e., gastric bypass or sleeve gastrectomy) from clinical files to avoid self-report bias.

An additional group of healthy volunteers are recruited from the community for comparison with patients.

The possibility of discontinuing participation at any time during the study is given to all participants. All data is de-identified.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Changes in preference (%) for the conditioned stimulus (CS+) according to intake (g) from pre- to post-conditioning. Intake % preference for CS+ is calculated as [CS+ intake/ (CS- + CS+ intake) *100] measured using the weight of stimulus consumed, in g at post-conditioning day (day 6) relative to pre-conditioning day (day 1)

Key secondary outcome(s))
1. Changes in preference (%) for CS+ according to pleasantness ratings (mm, gLMS) from pre- to post-conditioning. Pleasantness %preference for CS+ is calculated as [CS+ gLMS/ (CS- + CS+ gLMS) *100] measured using gLMS, in mm at post-conditioning day (day 6) relative to pre-conditioning day (day 1)
2. Striatal binding potential (BP) estimated as: (mean counts per voxel in the target area - counts per voxel in the reference region)/ counts per voxel in the reference region. The reference region is defined as a portion of the occipital lobe where D2 and D3 receptors are absent. The target area is defined as the striatum measured using IBZM single-photon emission computerized tomography (SPECT) on the post-conditioning day (day 6).

The following main explanatory (independent) variables are assessed on pre-conditioning day (day 1) and/or post-conditioning day (day 6):
1. Feeding behavior traits measured using The Dutch Eating Behavior Questionnaire (DEBQ)
2. Food Acceptance measured using the Food Action Rating Scale (FARS)

3. Hedonic hunger measured using the Power of Food Scale (PFS)
4. Addiction-like feeding behavior measured using the Yale Food Addiction Scale (YFAS)
5. Intensity and pleasantness ratings given to 4 concentrations of citric acid (sour), sodium chloride (salty), sucrose (sweet) and quinine hydrochloride (bitter) measured using general labelled magnitude/hedonic scales (gLMS/ gLHS)
6. Acuity in tastant identification (sour, salt, sweet and bitter) measured using a multiple forced-choice test
7. Taste Thresholds measured using electrogustometry
8. Hunger and thirst ratings (fasted and post-prandial) measured using gLMS and a visual analogue scale (VAS) on pre and post-conditioning days
9. Hunger and thirst ratings (fasted) measured using gLMS and VAS during the conditioning days

Completion date
12/07/2023

Eligibility

Key inclusion criteria
The inclusion criteria for the healthy group are:
1. Aged between 18 and 65 years old
2. General good health as determined by the investigator

The clinical sample consists of consecutive patients at a tertiary care outpatient centre specialised in the surgical treatment of obesity, belonging to Centro Hospitalar de Lisboa Ocidental, E.P.E., in Lisbon, Portugal. Patients are included in two groups: one group is of patients approved for bariatric surgery and on the waiting list (obese group) and the other is a group of patients that received bariatric surgery no less than 1.5 and no more than 4 years after either gastric bypass or sleeve gastrectomy (surgical group). In both groups, approval for bariatric surgery follows standard criteria as defined by the Portuguese National Health Service, namely:
1. Body mass index (BMI) greater than 40 Kg/m2 with or without associated comorbidities or greater than 35 Kg/m2 in the presence of at least 1 comorbidity (type 2 diabetes mellitus dyslipidemia, obstructive sleep apnea syndrome, obese hypoventilation syndrome, arterial hypertension or osteoarticular degenerative pathology, with marked functional limitation).
2. Age between 18 and 65 years
3. Failure of non-surgical interventions for weight reduction, for at least one year, obesity that is not secondary to an identified endocrine disease
4. Ability to understand the surgical procedure and to adhere to a long-term follow-up program
5. Absence of psychiatric disorders, absence of alcohol or drug dependence
6. Balanced relationship between operative risk and clinical risk

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit

18 years

Upper age limit
65 years

Sex
All

Total final enrolment
78

Key exclusion criteria
The exclusion criteria for healthy volunteers, assessed at entry into the study are:
1. Active acute respiratory infection
2. Active neurological or psychiatric disease
3. Active gastrointestinal, hepatic, or pancreatic disease
4. Diabetes
5. Illicit substance use or alcohol abuse
6. Use of any neuropsychiatric medication (including anxiolytics, antipsychotics, antidepressants, anticonvulsants, stimulants, anti-dementia medication, dopamine agonists and opioid pain relievers) or antidiabetic medication (including glp-1 agonists)
7. Obesity (BMI ≥ 30 Kg/m2) or underweight (BMI < 18.5 Kg/m2)
8. Illiteracy, or otherwise not understanding instructions for the study
9. Prior major gastrointestinal surgery and/or intra-gastric balloon in the previous 12 months
10. History of food allergies
11. Pregnancy or breastfeeding

Exclusion criteria for patients are equivalent to those mentioned above, except for obesity, and prior major gastrointestinal surgery (for the surgical group only).

Date of first enrolment
30/12/2016

Date of final enrolment
06/12/2021

Locations

Countries of recruitment
Portugal

Study participating centre
Champalimaud Research & Clinical Centre
Champalimaud Foundation
Avenida Brasília
Lisbon
Portugal
1400-038

Study participating centre
Hospital de Egas Moniz
Centro Hospitalar de Lisboa Ocidental E.P.E.
Rua da Junqueira, 126
Lisbon
Portugal
1349-019

Sponsor information

Organisation
Champalimaud Foundation

ROR
https://ror.org/03g001n57

Funder(s)

Funder type
Government

Funder Name
Fundação para a Ciência e a Tecnologia

Alternative Name(s)
Portuguese Science and Technology Foundation, Foundation for Science and Technology, Fundacao para a Ciencia e a Tecnologia, The Foundation for Science and Technology (FCT), FCT

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Portugal

Funder Name
Horizon 2020

Alternative Name(s)
EU Framework Programme for Research and Innovation, Horizon 2020 - Research and Innovation Framework Programme, European Union Framework Programme for Research and Innovation

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Funder Name
Fundação Champalimaud

Alternative Name(s)
Champalimaud Foundation, CF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Portugal

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during the current study will be available upon request from Prof Albino J. Oliveira-Maia, albino.maia@neuro.fchampalimaud.org

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		17/12/2024	19/12/2024	Yes	No
Preprint results		18/07/2023	08/01/2024	No	No