The effect of an encapsulated nutrient mixture on ileal brake activation: A double-blind randomized study to investigate the effects on body weight, food intake and satiety

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First part of study (Phase 1)Aim: To evaluate the efficacy of ileal brake activation, by ingestion of an encapsulated nutrient mixture delivered to the stomach (placebo) or distal small intestine (active) analysed by the amount of food consumed...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Appetite and general nutritional disorders
Study type	Interventional

Summary

ID

NL-OMON43989

Source
ToetsingOnline

Brief title
Proof of Concept study

Condition

- Appetite and general nutritional disorders

Synonym
Ileal brake activation and Weight loss

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Top Institute of Food and Nutrition;Wageningen

Intervention

Keyword: Encapsulated nutrient delivery, Ileal brake, Weight loss

Outcome measures

Primary outcome

First part of study (Phase 1)

Aim: To evaluate the efficacy of ileal brake activation, by ingestion of an encapsulated nutrient mixture delivered to the stomach (placebo) or distal small intestine (active) analysed by the amount of food consumed during a subsequent ad libitum meal.

Hypothesis: We hypothesize that delivery of encapsulated nutrient mixture to the distal small intestine (active) results in a reduction in food intake compared to encapsulated nutrient mixture delivery to the stomach (placebo).

Primary objective: To investigate whether delivery of an encapsulated nutrient mixture to the distal small intestine (active) decreases the amount of food consumed during a subsequent ad libitum meal compared to delivery of an encapsulated nutrient mixture to the stomach (placebo).

Main study (Phase 2)

Aim: To investigate the effect of six weeks ileal brake activation by nutrient delivery to the distal small intestine (active) on body weight. This will be

studied by daily ingestion of an encapsulated nutrient mixture which will be delivered to the distal small intestine (active) or stomach (placebo) before lunch and dinner for a period of 42 ± 2 days (6 weeks).
Hypothesis: We hypothesize that 6 weeks ileal brake activation by nutrient delivery to the distal small intestine (active) at lunch and dinner results in body weight reduction.
Primary objective: The difference in body weight before and after 6 weeks ileal brake activation by nutrient delivery to the distal small intestine (active; group 1) compared to nutrient mixture delivery to the stomach (placebo; group 2).

Secondary outcome

First part of study (Phase 1)

Secondary objective: To investigate whether intake of encapsulated nutrient mixture delivered to the distal small intestine (active) increases satiation compared to delivery of the encapsulated nutrient mixture to the stomach (placebo), as analysed by VAS-scores.
Tertiary objective: To analyse whether the appearance of glucose and insulin is delayed in plasma after encapsulated nutrient delivery to the distal small intestine (active) compared to encapsulated nutrient delivery to the stomach (placebo).

Main study (Phase 2)

Secondary objective: To investigate whether intake of encapsulated nutrient mixture delivered in the distal small intestine (active) decreases the amount of food consumed during a subsequent ad libitum meal compared to encapsulated nutrient mixture delivered in the stomach (placebo) in time, analysed pre-, middle and post intervention.

Tertiary objective: To investigate whether intake of encapsulated nutrient mixture (active) increases satiation analysed by VAS-scores compared to placebo pre, middle and post intervention.

Other objective(s): To evaluate effects of 6 weeks encapsulated nutrient delivery to the distal small intestine (active) on glucose and insulin plasma concentrations compared to nutrient delivery to the stomach (placebo). This will be analysed by monitor blood glucose and insulin responses in time pre- and post intervention.

Study description

Background summary

Obesity and weight management
Worldwide the incidence of overweight and obesity is rapidly increasing with negative impact on health and health care costs1. The efficacy of the currently available treatments is relatively limited on the long term2. So far, surgical intervention has been proven to be the only strategy to overcome severe obesity in the long-term3. Furthermore, in a recent meta-analysis it was concluded that dietary supplements and exercise alone does not contribute to improved weight loss after caloric restriction diets4. Therefore, it is important to develop new effective strategies that induce weight loss or help weight maintenance after weight loss. A promising mechanism for weight management is to activate the so called *ileal brake*.

Ileal brake
The ileal brake refers to an intestinal feedback mechanism that is triggered by

nutrients at a specific location in the small intestine, resulting not only in modulation of gastrointestinal secretions and motility but also of food intake and hunger5. The ileal brake can be activated by ileal infusion of undigested lipid6,7, and recently it was found that ileal infusion of sucrose and casein suppresses food intake to the same extend as equicaloric amount of lipids8. In addition to the reduction of food intake, an increase in feelings of satiety and decrease in hunger was found.
Since ileal brake activation seems to be a promising target for weight management strategies alternative nutrient delivery techniques have to be used. Several studies investigated the effects of nutrient infusion in all regions of the small intestine9. However all studies used intestinal feeding catheters in order to infuse nutrients directly into the desired part of the small intestine. In order to investigate the effect of long-term ileal brake activation in overweight individuals, a different approach for nutrient delivery needs to be chosen. An alternative for distal small intestinal nutrient delivery via feeding catheters is encapsulation of nutrients. Encapsulation can be used to deliver nutrients to a specific intestinal location. By encapsulation, nutrients are covered/surrounded with an edible coating. This coating is defined as a thin layer of edible material applied to the surface of the nutrients. This provides a barrier against digestion in the stomach and the proximal parts of the small intestine. Comparable approaches have already been used for site-specific drug delivery. Two examples of systems able to deliver drugs to the ileo-colonic region are the ColoPulse system described by Schellekens et al. (2010)10 and the ileo-colonic delivery system described by Varum et al. (2013)11. Both methods are invented to accelerate drug release in the ileo-colonic region and use specific Eudragit® polymer coatings. Adjusting these polymer coatings results in a more proximal (ileum) delivery. However these techniques were developed for drug delivery. To activate the ileal brake it is preferred to use a completely food grade application. Another food grade approach to deliver nutrients to the distal small intestine is micro-encapsulation. This micro-encapsulation technique will be used in the present study to deliver a mixture of nutrients consisting mostly sucrose (60%) , casein (30%) in a shell of whey protein (10%) to the distal small intestine.
The delivery method patented by AnaBio Technologies Ltd. (http://www.AnaBio.ie/) comprises an active component, encapsulated within a protein matrix of preferably whey protein. The mechanism by which their technique delivers the active to the preferred intestinal location is based on pH, surface porosity of the microspheres, and reaction to specific enzymes. These three parameters are used to design the micro-encapsulation beads to deliver the active ingredient to the preferred intestinal location (e.g. duodenum, jejunum or ileum). Furthermore the size of the micro-beads is important for intestinal transit time. AnaBio uses their data collected from human and animal studies to relate the size of the micro-beads to intestinal transit time, dose volume and physiological characteristics. The micro-bead size (micron range) can be chosen based on the population group and the required transit time, an average used size is 150 micron. The advantage of

these small particles is that the particles can be mixed with a food product. The ratio active : encapsulated protein matrix is 95 : 5%. This means that if sucrose will be encapsulated 95% of the micro-bead is pure sucrose and 5% is whey protein. We know from our previous research8 that infusion with 13 grams of sucrose is able to activate the ileal brake. For the present study we will use a mixture of encapsulated sucrose microbeats (60%) and encapsulated casein microbeats (30%) in order to simulate the composition of a small mixed carbohydrate and protein rich meal.

Efficacy small intestinal delivery
AnaBio provided data (which cannot be shared due to IP applications) of four in vivo studies of which 3 were human studies and 1 pig study. In these studies the efficacy of their delivery method has been investigated. It can be concluded from these studies that the whey protein micro-encapsulation technique is a specific intestinal delivery method for specific to either the ileum (2 human studies and 1 pig study) or the jejunum (1 human study).

Present study
In the present study the effect of 6 weeks ileal brake activation on body weight, BMI and waist circumference will be investigated. It is hypothesized that 6 weeks ileal brake activation by delivery of an encapsulated nutrient mixture to the distal small intestine results in reduced body weight. This will be studied by daily ingestion of an encapsulated nutrient mixture (e.g. 60% sucrose and 30% casein encapsulated in 10% whey protein) either delivered to the distal small intestine (active) or stomach (placebo) before lunch and dinner for 6 weeks in a randomized, double blind parallel placebo controlled trial. This will be studied in the second phase of the study (phase 2). Pre intervention, study day 1 and 2 (SD1 and SD2), middle (SD4) and post (SD5) intervention period the efficacy of the to decrease food intake (>68 kcal) will be evaluated.
It is unknown whether the ileal brake will be activated by the encapsulated nutrient mixture delivered to the distal small intestine (active) to the same magnitude as ileal brake activation by ileal sucrose and casein infusion. Therefore, we will study the ileal brake activation efficacy of the encapsulated nutrient mixture ingestion on ad libitum food intake. This will be done in the first phase of the study (phase 1). Pre-intervention the efficacy will be tested in a randomized placebo controlled cross over design. Within every subject the difference in ad libitum food intake after active or placebo ingestion will be studied. If the active encapsulated nutrient mixture does not result in a reduction of food intake the intervention will not start.

Study objective

First part of study (Phase 1)
Aim: To evaluate the efficacy of ileal brake activation, by ingestion of an

encapsulated nutrient mixture delivered to the stomach (placebo) or distal small intestine (active) analysed by the amount of food consumed during a subsequent ad libitum meal.
Hypothesis: We hypothesize that delivery of encapsulated nutrient mixture to the distal small intestine (active) results in a reduction in food intake compared to encapsulated nutrient mixture delivery to the stomach (placebo).
Primary objective: To investigate whether delivery of an encapsulated nutrient mixture to the distal small intestine (active) decreases the amount of food consumed during a subsequent ad libitum meal compared to delivery of an encapsulated nutrient mixture to the stomach (placebo).
Secondary objective: To investigate whether intake of encapsulated nutrient mixture delivered to the distal small intestine (active) increases satiation compared to delivery of the encapsulated nutrient mixture to the stomach (placebo), as analysed by VAS-scores.
Tertiary objective: To analyse whether the appearance of glucose and insulin is delayed in plasma after encapsulated nutrient delivery to the distal small intestine (active) compared to encapsulated nutrient delivery to the stomach (placebo).

Main study (Phase 2)
Aim: To investigate the effect of six weeks ileal brake activation by nutrient delivery to the distal small intestine (active) on body weight. This will be studied by daily ingestion of an encapsulated nutrient mixture which will be delivered to the distal small intestine (active) or stomach (placebo) before lunch and dinner for a period of 42 ± 2 days (6 weeks).
Hypothesis: We hypothesize that 6 weeks ileal brake activation by nutrient delivery to the distal small intestine (active) at lunch and dinner results in body weight reduction.
Primary objective: The difference in body weight before and after 6 weeks ileal brake activation by nutrient delivery to the distal small intestine (active; group 1) compared to nutrient mixture delivery to the stomach (placebo; group 2).
Secondary objective: To investigate whether intake of encapsulated nutrient mixture delivered in the distal small intestine (active) decreases the amount of food consumed during a subsequent ad libitum meal compared to encapsulated nutrient mixture delivered in the stomach (placebo) in time, analysed pre-, middle and post intervention.
Tertiary objective: To investigate whether intake of encapsulated nutrient mixture (active) increases satiation analysed by VAS-scores compared to placebo pre, middle and post intervention.
Other objective(s): To evaluate effects of 6 weeks encapsulated nutrient delivery to the distal small intestine (active) on glucose and insulin plasma concentrations compared to nutrient delivery to the stomach (placebo). This will be analysed by monitor blood glucose and insulin responses in time pre- and post intervention.

Study design

First part of study (Phase 1)

Study design: Randomized placebo controlled double blind cross-over study.
Go/no go: After phase 1 has been completed, a go/no go decision will be taken, before the start of phase 2. In case of a significant decrease (>68 kcal) in ad libitum food intake after ingestion of the active (phase 1) we will continue with phase 2. If ad libitum food intake is not decreased (>68 kcal) after ingestion of the active in phase 1, phase 2 will not be conducted.

Main study (Phase 2)

Study design: Randomized placebo controlled double blind parallel intervention trial.
Main study parameters/endpoints: Difference in body weight and BMI before and after the intervention between the placebo group and the intervention group.

Intervention

Ingestion of micro encapsulated casein and sucrose (ileal delivery)

Study burden and risks

Blood sampling: on each test day (test day 1-4) a flexible intravenous cannula (Biovalve 1,0mm) is inserted into an antecubital vein in the fore-arm for blood sampling. Per time point 8mL of blood is drawn, totalling 72mL per test day (with a total of 288mL for the 4 test days). After collection (immediately after collection DPP-IV inhibitor will be added to the tube), K2EDTA tubes will be centrifuged at 2500 rpm for 10 min at 4°C. The supernatant will be collected and this will be centrifuged again at 4000 rpm for 10 min at 4°C. Plasma will be collected in 1-mL aliquots and stored at -80°C until analysis. During blood sampling, the volunteers will remain seated in a comfortable chair, with an adjustable back. No side effects are expected when sampling blood in this manner.

VAS scores for satiety and GI symptoms Scores for satiety feelings (e.g., satiety, fullness, hunger, prospective feeding, desire to eat, desire to snack) and gastrointestinal symptoms (burning, bloating, belching, cramps, colics, warm sensation, sensation of abdominal fullness, nausea and pain) will be measured using Visual Analogue Scales (VAS, 0 to 100 mm) anchored at the low end with the most negative or lowest intensity feelings (e.g., extremely unpleasant, not at all), and with opposing terms at the high end (e.g., extremely pleasant, very high, extreme). Volunteers will be asked to indicate on a line which place on the scale best reflects their feeling at that moment. The scoring forms will be collected immediately so that they cannot be used as

a reference for later scorings.

Ingestion of micro encapsulated nutrients: We don't expect any problems with ingestion of micro encapsulate since it is very easy to swallow and easy to mix with other food products (yoghurts, drinks etc).

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

* Based on medical history and previous examination, no gastrointestinal complaints can be defined.
* Age between 18 and 65 years. A higher age comes with a higher chance of comorbidities. These could influence our study outcomes and therefore this age range was chosen. This study will include healthy adult subjects (male and female). Women must be taking

contraceptives (only needed in women with childbearing potential)
* BMI between 25 -30 kg/m2
* Normal Dutch eating habits eating three meals a day including breakfast as assessed by an validated questionnaire
* Voluntary participation
* Able to participate in the study, willing to give informed consent and to comply with the study procedures and restrictions

Exclusion criteria

* History of severe cardiovascular, respiratory, urogenital, gastrointestinal/ hepatic, hematological/immunologic, metabolic/nutritional, endocrine, neurological/psychiatric diseases, allergy, major surgery and/or laboratory assessments which might limit participation in or completion of the study protocol. The severity of the disease (major interference with the execution of the experiment or potential influence on the study outcomes) will be decided and documented by the principal investigator.
* Use of any medication, except oral contraceptives, which may interfere with this study (major interference with the execution of the experiment or potential influence on the study outcomes). This has to be decided and documented by the principle investigator.
* Administration of investigational drugs or participation in any scientific intervention study which may interfere with this study, to be decided by the principle investigator, in the 90 days prior to the study.
* Major abdominal surgery interfering with gastrointestinal function (uncomplicated appendectomy, cholecystectomy and hysterectomy allowed, and other surgery) upon judgement of the principle investigator.
* Dieting (medically prescribed, diabetic and vegetarian)
* Pregnancy, lactation
* Excessive alcohol consumption (>20 alcoholic consumptions per week)
* Intention to stop smoking
* Self-admitted HIV-positive state
* * Above average score (>3.39 for female and >2.89 for male) on the restrained eating scale of the Dutch Eating Behaviour Questionnaire
* Reported unexplained weight loss or gain of >4 kg in the month prior to screening

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-12-2015
Enrollment:	72
Type:	Actual

Ethics review

Approved WMO Date:	20-05-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-04-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL51990.068.14