The effect of different macronutrients on the ileal brake

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Hypotheses: - Ileal delivery of casein and/or sucrose induces stronger effects on satiation compared to placebo- Ileal delivery of casein induces stronger effects on satiation than ileal fat delivery- Ileal delivery of sucrose induces stronger...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON37970

Source
ToetsingOnline

Brief title
Macronutrients and the ileal brake

Condition

- Other condition
- Appetite and general nutritional disorders

Synonym
Obesity and overweight

Health condition

Obesitas

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Carbohydrate, Ileal brake, Infusion, Protein

Outcome measures

Primary outcome

Main study parameter/endpoint

- Difference in satiation (as measured by VAS) per time points and difference

in food intake as measured during an ad libitum meal

Secondary outcome

Secondary study parameters/endpoints

- Measurements in plasma and/or platelet poor plasma Plasma levels of the gut

hormones Cholecystokinin (CCK), Glucagon Like Peptide-1 (GLP-1) and peptide YY

(PYY)

Other study parameters:

- Gastric emptying by using the C13 stable isotope breath test

- Small bowel transit time by using lactulose hydrogen breath test

- Gallbladder emptying by gallbladder ultrasound

Study description

Background summary

Nutrient sensing can be defined as the ability to sense available nutrients and to generate a physiologically adequate regulatory response to these macronutrients involving adequate digestion and regulation of food intake. Various physiological signals are involved in nutrient sensing, such as humoral, neural, microbial and mechanical signals. It is clear that nutrient sensing composes of a cascade of events. The densely innervated stomach contributes to the initial feelings of satiation1. The subsequent release of ingesta into the duodenum leads into a staggered release of hormones and other substances, and direct or indirect neural activation all regulating meal initiation, meal termination and digestion of nutrients.

The appearance of the food matrix into the duodenum, both during a meal and during the postprandial phase results in a feed-back from different parts of the intestine to the stomach, to the small intestine and to the central nervous system. All these processes inhibit, in concert, food processing in the gastrointestinal tract, satiation and appetite sensations and, consequently, food intake. These processes are involved in the so-called intestinal brake. The location at which the feedback process is initiated determines the severity of the brake effect; the entry of nutrients into the duodenum and jejunum activates the so-called duodenal and jejunal *brakes*: negative feedback mechanisms that influence the function of more proximal parts of the gastrointestinal tract. Activation of both of these feedback mechanisms results in reduction of food intake and inhibition of hunger, probably partly by inhibition of gastric emptying rate (thus contributing to enhanced and prolonged gastric distension)2-6 and small intestinal transit time. More distal in the small intestine, the ileal brake is a feedback mechanism that results in inhibition of proximal gastrointestinal motility and secretion and increase feelings of satiation and reduction of ad libitum food intake7-11.These results all point to a potentially powerful role of the ileal brake in the regulation of digestion, with direct or indirect impact upon eating behaviour and satiation. The inhibitory effect of an intestinal brake, which can either be a duodenal, jejunal or ileal brake, activation on satiation has been repeatedly demonstrated, but it is uncertain whether this effect results from direct stimulation of central satiation centres in the brain (directly due to CCK or afferent signalling of the N. Vagus), or whether the brake effect on hunger and satiation is achieved indirectly via the delay in gastric emptying. Also, the sensing mechanisms of nutrients in the gut, which eventually lead to the intestinal *brakes* are largely unknown, but involve a variety of mucosal receptors. These receptors include for example, G-protein gustducin and G-protein-coupled receptors, TRPV1, taste receptros and various other types including melanocortin, opioid and PPAR

The current scientific data strongly suggest that activation of the ileal brake provides the most powerful feedback mechanism to gastrointestinal transit and, especially, satiety signals and food intake12, 13, 14 . Most studies have used fat as macronutrient. The effects of several amounts, types and preparations of fat on the ileal brake have previously been investigated and reported. We can

conclude that the ileal brake seems to induce stronger effects on gut function, satiation and meal intake than the duodenal- and jejunal brake, when fat is the brake substrate. Furthermore infusion of fat in the ileum induces stronger effects when compared to oral ingestion. No dose-response effects were observed in a human study to the effects of 3- and 9 g intra-ileal fat, respectively, the higher dosage of fat seems to be appropriate to clearly establish an ileal brake effect. Poly-unsaturated fat has stronger effects than saturated fat; small fat droplets are more powerful to invoke the ileal brake than larger droplets. The most potent fatty acid for ileal brake induction appears to be C18:2 7, 8, 12.

As shown above, fat is rather extensively been studied in humans, but much less is known about proteins and carbohydrates. As such, fat may serve as a positive control in ileal brake studies. Until present, the effects of the other macronutrients to induce the ileal brake remain largely unknown. There is evidence that carbohydrates induce the ileal brake13-15. Infusion of glucose into the small intestine, at a rate mimicking the overall gastric emptying rate of 2-3 kcal/min, reduces hunger and desire to eat, increases fullness and reduces subsequent food intake16. Furthermore, infusion of glucose also inhibits gastric emptying and increases pancreatic and intestinal secretion16, 17.
Proteins may also exert effects, although data are scarce and not convincing15, 18. However, it becomes more and more accepted that proteins may induce stronger effects on satiation and food intake than fat or carbohydrates. Recently, researcher at Wageningen University conducted an in vivo study in pigs (manusscript in preparation). They infused different nutrients into the pig ileum and collected portal blood for CCK, GLP-1 and PYY analysis and measured food intake. They found that infusion of the protein casein and the carbohydrate sucrose induced the highest release of satiety hormones (CCK, GLP-1) and reduced food intake in pigs. Different studies, in both humans and animals showed that oral ingestion of casein and sucrose induced satiety hormone release reduced daily food intake, acid secretion and duodenal motor activity. These new data validate our choise of using casein and sucrose in this human in vivo study.

Study objective

Hypotheses:
- Ileal delivery of casein and/or sucrose induces stronger effects on satiation compared to placebo
- Ileal delivery of casein induces stronger effects on satiation than ileal fat delivery
- Ileal delivery of sucrose induces stronger effects on satiation than ileal fat delivery

Primary objective:
• To assess the effect of casein and sucrose delivered to the ileum on satiation

Secondary objectives:
• To investigate the effect of ileal delivery of casein and sucrose on ad libitum meal intake.
• To asses the effect of casein and sucrose delivered to the ileum on gastric emptying rate
• To compare the different effects of casein, sucrose and safflower oil on small bowel transit time
• To asses the effect of casein and sucrose delivered to the ileum on gallbladder volumes

Study design

This study is designed as a double-blind randomized cross-over study with six different treatments (casein (high and low dose) / sucrose (high and low dose) / safflower oil (positive control)/ saline (placebo)).

Intervention

Healthy volunteers will compleet 6 test days in total. Every test day another substance will be infused into the ileum via the nasoileal catheter:
casein (high and low dose), sucrose (high and low dose), safflower oil (positive control) and saline (placebo)
Infusion is via the nasoileal catheter which will be inserted on monday (test days are on tuesday, wednesday and thursday). Every morning starts with checking the position of the catheter. If the position in the ileum is confirmed, the test day can start. After the third test day (thursday) the nasoileal catheter will be removed. The same volunteer will undergo the similar tests a week later (after wash-out period of 4 days). In week 2, casein will be switched for sucrose and the negative control (placebo) will be switched for a positive control (safflower oil). Randomisation determines the order of these infused solutions.

Study burden and risks

3 Short visits (1 hour each): screening, study day 1 and study day 2 (both insertion of nasoileal catheter)
6 Longer visits (4 hours each): test day 1,2,3 and test day 4,5,6

Blood sampling
On each test day (test day 1-6), after the position of the ileal catheter has

been confirmed by fluoroscopy, 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 88ml per day (total of 264 mL for the 3 test days in week 1). Before the start of test week 2, haemoglobin and haematocrit are determined to ensure normal values of both substances. Test week 2 can start if both parameters are in the normal range. After collection, one K2EDTA tube will be centrifuged at 2600 rpm for 20 min at 20°C. The other K2EDTA will be centrifuged at 2500 rpm for 15 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. The blood samples that are not used during the analysis of this study will be stored and kept for a maximum period of ten years. The tubes will be coded, and the code will be kept by prof. dr. A.A.M Masclee, the principal investigator. This enables us to do further analysis within the aim of this protocol.

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. Before the start of test week 1 and test week 2, haemoglobin and haematocrit are determined to ensure that these parameters are in normal range

Gastric emptying rate
Gastric emptying of the test meal will be determined by using a 13C stable isotope breath test.
13C-octanoic acid (100 mg, Campro Scientific bv, Veenendaal the Netherlands) will be mixed into the standardized breakfast test meal ingested at t=0. Breath samples of 13CO2 will be collected from volunteers by breathing into a re-usable plastified aluminium bag at baseline (immediately before consumption of the test product, t = -15 minutes) and between 15 and 240 min after start of the treatment. Actual time at which the breath sample is collected will be registered and will be used in the kinetic evaluation. Samples will be collected, stored and afterwards analysed using Isotope Ratio Mass Spectometry (Finnigan MAT 252).

Gastric emptying rate will be determined by using a 13C stable isotope breath test. The 13C octanoid acid breath test is a reliable and safe test for measuring the gastric emptying rate of solid meals. It is widely used and even possible to use in children and pregnant women. Therefore we don*t expect any side effects.

Small bowel transit time
Duodeno-caecal transit measurement will be performed by lactulose hydrogen breath analysis, as described by Ledeboer et al. Via an opening of the catheter located in the duodenum 6 g of lactulose (Legendal, Inpharzam, Amersfoort) is administered at t=30 min together with the start of ileal infusion. Samples of

end-expiratory breath are taken under basal conditions and at 10 min intervals during the first hour and at 15-30 min intervals during the second, third and fourth hour after meal ingestion with lactulose administration. The samples are directly analysed using a handheld hydrogen breath test unit. Small bowel transit time is defined as the time between lactulose administration and the onset of a sustained rise in breath hydrogen concentration of at least 10 parts per million (ppm) above basal level.

Together with the start of the ileal infusion, 6g of lactulose will be infused in the duodenum to measure small bowel transit time. This method, first described by Bond et al, appears to provide a simple, safe and non-invasive means of studying small bowel transit time in healthy humans.

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.

Gallbladder ultrasound
Gallbladder (GB) volumes will be measured in volunteers by real-time ultrasonography (Technos, 3.5 MHz transducer) (see study design for measurement frequency). GB volume will be calculated by the sum of cylinders method using a computerized system. In this method, the longitudinal image of the gallbladder is divided into series of equal height, with diameter perpendicular to the longitudinal axis of the gallbladder image. The uncorrected volume is the sum of volumes of these separate cylinders. To correct for the displacement of the longitudinal image of the gallbladder from the central axis, a correction factor is calculated from the longitudinal and transversal scans of the gallbladder. Gallbladder volume is calculated by multiplication of the uncorrected volume with the square of the correction factor. This is done automatically by the computer connected to the echoscope. The mean of the two measurements will be used for analysis. The assumptions and the mathematical formula used to calculate gallbladder volume have been described and validated previously

Echoscopy of the gallbladder is not associated with any risks.

Catheter placing and fluoroscopy
The subjects will perceive mild discomfort during the placement of the catheter. The radiation exposure during the positioning of the feeding tube is minimal (0.06 mSv). Each test day starts with checking the position of the tube. The radiation exposure of this procedure is minimal as well (0.01 mSv). The total exposure to radiation (during all test days) will be approximately 0.18 mSv (0.06 mSv + 0.06 mSv + 0.06 mSv) , which equals the radiation, which is received during a three-hr flight in an aeroplane at a 4-km altitude (www.nrg-nl.com).

All participants are healthy volunteers and we don't expect any health benefits or disadvantages.

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

1) Based on medical history and previous examination, no gastrointestinal complaints can be defined.
2) Age between 18 and 55 years. This study will include healthy adult subjects (Male and Female). Women must be taking oral contraceptives
Subjects over 55 years have an increased risk for comorbidities, therefore, subjects over 55 years will not be included.
3) BMI between 18 and 29 kg/m2
4) Less then 2 *yes* responses in the SCOFF questionnaire (see appendix F1)
5) Weight stable over at least the last 6 months

Exclusion criteria

1) History of severe cardiovascular, respiratory, urogenital, gastrointestinal/ hepatic, hematological/immunologic, HEENT (head, ears, eyes, nose, throat), dermatological/connective tissue, musculoskeletal, 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 by the principal investigator.
2) Use of medication, including vitamin supplementation, except oral contraceptives, within 14 days prior to testing
3) 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 180 days prior to the study
4) Major abdominal surgery interfering with gastrointestinal function (uncomplicated appendectomy, cholecystectomy and hysterectomy allowed, and other surgery upon judgement of the principle investigator)
5) Dieting (medically prescribed, vegetarian, diabetic, macrobiological, biological dynamic)
6) Pregnancy, lactation
7) Excessive alcohol consumption (>20 alcoholic consumptions per week)
8) Smoking
9) Blood donation within 3 months before the study period
10) Self-admitted HIV-positive state
11) Eating disorders detected using the *SCOFF questionnaire* (in Dutch translation)
12) Lactose or Cow milk intolerance

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-04-2012
Enrollment:	17
Type:	Actual

Ethics review

Approved WMO Date:	30-06-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-03-2012
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	NL36916.068.11

Study results

Date completed:	07-04-2013
Actual enrolment:	17