The ex vivo effect of bitter, sweet, salt, umami and sour tastants on the release of gastrointestinal satiety peptides

Published: 28-12-2011
Last updated: 29-04-2024

Hypotheses: - The five tastants (sour, sweet, salt, bitter and umami) each induce GI peptide release by human duodenal mucosa ex vivo. - The five tastants (sour, sweet, salt, bitter and umami) each induce GI peptide release by human ileal mucosa ex...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON36190

Source
ToetsingOnline

Brief title
Ex vivo tastants and GI peptide release

Condition

- Other condition
- Appetite and general nutritional disorders

Synonym
satiety and obesity

Health condition

obesitas

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Ex vivo, Tastants, Taste receptors, Ussing chamber

Outcome measures

Primary outcome

Main study parameters/endpoints

- Measurements in serosal samples of the gut hormones Cholecystokinin (CCK), Glucagon Like Peptide-1 (GLP-1) and Peptide YY (PYY) (in pmol/mL) from human duodenal biopsies in the Ussing chamber

- Measurements in serosal samples of the gut hormones Cholecystokinin (CCK), Glucagon Like Peptide-1 (GLP-1) and Peptide YY (PYY) (in pmol/mL) from human ileal biopsies in the Ussing chamber

Secondary outcome

-

Study description

Background summary

The gastrointestinal tract generates many signals that play a role in the regulation of eating behavior, most importantly satiety signals. The gut is therefore an appealing target for food products to induce satiety and reduce food intake. Gut peptides, such as cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1), have been demonstrated to reduce food intake and hunger after intravenous administration1-3. However, because of incoherent results between studies there is still controversy about the effect of the release of

satiety peptides on food intake. On the other hand, long-term use of a GLP-1 agonist has been shown to reduce body weight in obese individuals4. Together these results illustrate the potential of targeting the gastrointestinal tract in weight management and weight loss strategies.

In order for different nutrients to influence hunger/satiety, the presence of these nutrients in the small intestine has to be sensed. There appear to be two major principles of nutrient sensing in the gastrointestinal tract5. Firstly, nutrients or their direct breakdown products can interact with receptors on the microvilli of enteroendocrine cells. These enteroendocrine cells respond by secreting mediators including cholecystokinin (CCK), Peptide YY (PYY) and Glucagon Like Peptide-1 (GLP-1) which are either transported through the blood stream or activate their receptors on vagal nerve endings. In parallel, a second mechanism is operating. Nutrients (lipids, amino acids) are taken up by enterocytes, which for example form lipid-derived mediators. These mediators also interact with receptors on vagal nerve endings. In other words, nutrient sensing is primarily mediated by enteroendocrine cells individually scattered in the lining of the epithelium.

Enteroendocrine cells express various specific luminal receptors. These receptors may activate intracellular pathways through direct gating of ion channels, but recently, there has been a growing interest in the G-protein coupled receptors (GPCR*s) such as the G-protein gustducin. These recently discovered receptors include GPR119, GPR93, GPR55, GPR120, GPR40, TRPV1 and various other types6, 7. Different nutrients such as free fatty acids and peptides can be recognized by these receptors. Activation of these receptors leads to an intracellular signaling cascade which results in the release of gastrointestinal mediators.

Taste refers to five basic oral perceptions: sweet, salty, sour, bitter and umami. Nutrients are initially detected in the mouth by interacting with different transduction elements, including ion channels and GPCRs that are expressed in the apical membranes of specialized epithelial cells, known as taste receptor cells. Recently the sensors detecting sweet and bitter sensations and amino acids have been identified and characterized as unrelated GPCR families: the T1R (sweet and amino acids) and T2R (bitter) receptor families. Several investigators reported the expression of bitter, sweet and umami taste receptors in the gut. Bezencon et al showed that T1R1, T1R2, T1R3, α-gustducin and TRPM5 are expressed in the stomach, small intestine and colon of humans8. Activation of the taste receptor-signalling molecules, which are expressed in entero-endocrine cells (EEC), by luminal content induces an increase in intracellular Ca^{2+}, which triggers the release of peptides like PYY, GLP-1 or CCK. If this could be confirmed in humans, tastants possibly could be used in weight management and weight loss strategies

Chen et al showed that addition of the bitter stimulus denatonium benzoate (DB) increased the intracellular Ca^{2+} in STC-1 cells, leading to CCK release9. This

fits with the strong CCK-stimulating ability of proteins, which are generally perceived as having a bitter compound. Geraedts et al showed that bitter, sour and sweet tastants induce the largest effect on CCK release in the STC-1 cell line10. In humans, the precise effect of stimulating taste receptors in the small intestine is unknown and the release of gut derived satiety peptides in response to bitter and sour stimuli could play a role in protecting against potentially toxic (bitter) substances.

It is known that the appearance of certain nutrients in the small intestine results in a negative feedback mechanism from different parts of the intestine to the stomach, the small intestine and to the central nervous system. These processes inhibit food processing, appetite sensations and food intake, and furthermore they increase feelings of satiety and satiation. It was shown that the ileal brake induced stronger effects on gut function than the duodenal or jejunal brake when fat was used as a brake substrate. Since taste receptors were found in the small intestine, infusion of different tastants directly into the small intestine could result in the activation of an intestinal brake or the release of satiety peptides. Therefore we would like to investigate the effects of representatives of the five tastants (sweet, salty, sour, bitter and umami) on the ex vivo release of the gut satiety peptide CCK and GLP-1. First we will use duodenal tissue to confirm the release of gut satiety peptides. The duodenum is the first small bowel part to sense nutrients upon oral ingestion. When positive results with tastants have been obtained (release of gut peptides) in the duodenum, the procedure will be extended to distal ileum tissue. We anticipate, based on the strong inhibitory effect of the ileal brake on satiety in humans in vivo, that this effect is even more pronounced than in the duodenum.

This will be investigated by using the Ussing chamber. The Ussing chamber was first described in 1951 by the Danish physiologists Ussing and Zerhan. This technique enables to study vital tissue outside of the body for several hours, and has many applications. It is mostly used to study ion transport, drug and protein absorption, and several pathophysiological processes both in animals and humans. Additionally, it provides a suitable model to study effects of a variety of compounds on intestinal tissue secretions. The Ussing chamber can be used to (simultaneously) study different types of substances and this makes it a fast, non-invasive and low cost screening method. Our group showed previously that different types of proteins exert different effects on the release of CCK and GLP-1 by human intestinal mucosa11. We also validated the use of the Ussing chamber to study satiety hormone release8 by intestinal mucosa. The results of this study will be used to design a follow-up human in vivo experiment, targeting the ileal brake with tastants.

Study objective

Hypotheses:
- The five tastants (sour, sweet, salt, bitter and umami) each induce GI

peptide release by human duodenal mucosa ex vivo.
- The five tastants (sour, sweet, salt, bitter and umami) each induce GI peptide release by human ileal mucosa ex vivo.
- Denatonium benzoate (bitter) induces the largest effects on the release of gut derived satiety peptide hormones.
- The five tastants induce different larger effects (higher release of CCK, GLP-1 and PYY) on proximal distal (duodenumileum) versus than distal proximal (ileumduodenum) parts of the human small intestine. of the human

Primary objective:
• To assess the effect of sour, sweet, salt, bitter and umami tastants on the release of satiety hormones (CCK, GLP-1 and PYY) in human duodenal mucosa ex vivo

• To assess the effect of sour, sweet, salt, bitter and umami tastants on the release of satiety hormones (CCK, GLP-1 and PYY) in human ileal mucosa ex vivo

Secondary objective:
• To investigate the effect of the five tastants on different parts (duodenum and ileum) of the human small intestine

Study design

This study is designed as an observational study with invasive measurements

Intervention

Patients undergo gastroduodenoscopy/colonoscopy for a medical reason. If a patient decides to participate in this study, 6-8 biopsies of the duodenom or ileum will be taken if no relevant abnormalities are found during endoscopy. This is the only difference with the regular procedure.

Study burden and risks

All patients undergo gastroduodenoscopy or colonoscopy for a medical reason. Only difference with regular procedure is taking 6-8 extra biopsies at the end of the procedure. This will extend the duration of the endoscopies with 2-3 minutes.

Gastroduodenoscopy
The gastroduodenoscopy, performed by a gastroenterologist, is a standard procedure that takes 10 to 20 minutes. These patients have a medical indication to undergo a gastroduodenoscopy. The only difference, with the standard procedure, is that 6-8 extra biopsies will be taken (with a standard biopsy forceps). Diagnostic upper GI endoscopy is a remarkably safe procedure. One large US study estimated an overall complication rate (including mucosal

biopsy) of 0.13% and an associated mortality of 0.004%. Taking the additional biopsies will be the only extra risk for the patient. We would like to include patients who already need to undergo a gastroduodenoscopy for a medical reason. By this mean we can diminish the risk of a gastroduodenoscopy for healthy volunteers.

Colonoscopy
In patients undergoing colonoscopies for a medical reason (which is the case in the patients used in this study), there is a very small risk (ranging from 0.016-%0.2%) of bowel perforation. Shiffman et al conducted a study on the risk of bleeding after endoscopic biopsy or polypectomy. They found that 4.6% of all patients (32 of 694) reported bleeding, 28 had a minor and self-limited, clinically insignificant bleeding and 4 (0.58%) had a major bleeding which required hospitalization or treatment. All 4 of these patients had undergone colonic polypectomy. Since the colonoscopy in these patients is performed because of medical reasons (not for research reasons), the patients will be informed about these risks by the gastroenterologist. We are taking a few extra small biopsies (with standard forceps), and therefore we expect that the risk of adverse events because of these extra biopsies would be much lower than 0.58%

Contacts

Public
Universiteit Maastricht

Universiteitssingel 40
6229ER Maastricht
NL
Scientific
Universiteit Maastricht

Universiteitssingel 40
6229ER Maastricht
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

3.1.2 Inclusion criteria for first part of study (duodenal biopsies):
- Step 1 (patients asked for participation):
1) Patients (male and female between 18 and 65 years) referred for upper GI endoscopy (because of functional complaints)
1)2) Based on medical history and previous examination, no objection arises for taking extra biopsies during the gastroduodenoscopy. or colonoscopy.
- Step 2 (patients agreed to participate and in who biopsies will be taken)
1) Patients with no relevant endoscopic abnormalities (gastroduodenoscopy): patients without gastric or duodenal ulcers/polyps/lesions suspect for malignancy and esophageal lesions or varices.;2) Based on medical history and previous examination, no objection arises for taking extra biopsies during the colonoscopy
- Step 2 (patients agreed to participate and in who biopsies will be taken)
2) Patients with no relevant endoscopic abnormalities (colonoscopy): patients without ileal and/or colonic ulcers/polyps/diverticula and lesions suspect for malignancy

Exclusion criteria

1) History of severe cardiovascular, gastrointestinal/ hepatic, hematological/immunologic, metabolic/nutritional disease and/or laboratory assessments which might limit participation in the study. 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, which could interfere with normal coagulation (anticoagulants, antiplatelet drugs).
3) Major abdominal surgery interfering with gastrointestinal function (uncomplicated appendectomy, cholecystectomy and hysterectomy allowed, and other surgery upon judgement of the principle investigator)
4) Excessive alcohol consumption (>20 alcoholic consumptions per week)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	16-01-2012
Enrollment:	80
Type:	Anticipated

Ethics review

Approved WMO

Date:	28-12-2011
Application type:	First submission
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC 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	NL37106.068.11