The identification and spatial distribution of different nutrient receptors along the gastrointestinal tract

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Hypotheses: - The nutrient sensing receptors have a different spatial distribution along the intestinal tract.- The receptors: T1R2/T1R3, SGLT-1, G-protein coupled receptor 120, T1R1/T1R3, Pept1, G-protein coupled receptor 93, calcium sensing...

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

Summary

ID

NL-OMON37661

Source
ToetsingOnline

Brief title
Identification of nutrient receptors GI tract

Condition

- Other condition
- Appetite and general nutritional disorders

Synonym
obesity and overweight

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: Distribution, Gastrointestinal tract, Identification, Nutrient receptors

Outcome measures

Primary outcome

Primary objective:

To assess the expression of nutrient sensing receptors at various specific

sites along the intestinal tract.

Secondary outcome

Secondary objective:

To investigate the cellular localization, namely on endocrine cells or vagal

nerve endings of the nutrient sensing receptors at various specific sites along

the intestinal tract.

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, like cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) are important mediators of the satiety signalling. CCK and GLP-1 have been demonstrated to reduce food intake and hunger after intravenous administration [1-3]. Long-term use of a GLP-1 agonist has been shown to reduce body weight in obese individuals [4]. 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 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 tract [5]. Firstly, nutrients or their direct breakdown products in the lumen of the gut can interact with receptors on the microvilli of enteroendocrine cells. These enteroendocrine cells respond by basal side secretion of 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, where they can subsequently be converted to nutrient-derived mediators. These mediators also interact with receptors on vagal nerve endings.

Many different receptors have been suggested to be involved in the sensing of carbohydrates, proteins and fats. We would like to investigate those receptors potentially involved in satiety signalling. For carbohydrates the sweet receptor and glucose transporter have been suggested to induce GLP-1 secretion. The sweet receptor, a heterodimer of T1R2 and T1R3, has been observed to be located on the enteroendocrine cells of the gastrointestinal tract [6-8]. However, this might not be the sole carbohydrate sensing receptor. The glucose transporter, SGLT-1, is also involved in GLP-1 secretion in response to glucose [9].
G-protein coupled receptor 120 has been described as an important fatty acid sensing receptor in the gastrointestinal tract. Activation of this receptor results in GLP-1 and CCK secretion [10, 11].
Proteins and amino acids are more potent in inducing a satiety signal then carbohydrates and fat, therefore we would like to investigate the distribution of several potential protein sensing receptors [12]. The oligopeptide transporter, Pept1, is highly expressed in the small intestine of humans and has been implicated to be essential for the stimulation of the vagal nerve in response to peptides [13]. Also the umami receptor, a heterodimer of T1R1 and T1R3, is expressed in the intestine. Other potential peptide sensing receptors, which have not been investigated in the human intestine, are G-protein coupled receptor 93, the calcium sensing receptor and the G-protein coupled receptor C6A. These are found in the gastrointestinal tract of rodents and observed to induce GLP-1 or CCK secretion in enteroendocrine cells lines [14].
As mentioned before, not only nutrients but also their derivates are able to induce satiety. The receptors implicated to be involved in sensing these derivates are the cannabinoid receptor 1 and the G-protein coupled receptor 119 [15, 16].
Apart from the nutrient sensing receptors we would like to investigate the receptors for CCK and GLP-1, these receptors are important in the further signalling of the satiety signal via the vagal nerve towards the brain [17].

Investigating which receptors are involved in the nutient sensing of enteroendocrine cells and on nerve endings, gives further knowledge on the kind of nutrients responsible for the secretion of gut hormones involved in satiety

signalling. So far only little is know about the distribution of potential nutient sensing receptors along the gastrointestinal tract. We are interested in the intestinal parts which highly secrete CCK and GLP-1 [18, 19]. By comparing these tissues, it is expected to further elucidate which receptors are important for satiety signalling in the intestine.
Having this information gives rise to further reseach on how these receptors stimulate the secretion of gut hormones. Moreover, knowing which receptors are involved in satiety signalling, gives oppertunity for targeting these receptors to increase satiety and influencing food intake.
We aim to investigate the distribution of the above mentioned receptors in the following referred to as *nutrient sensing receptors*, which have been suggested to be involved in satiety signalling. For these receptors the gene expression, localisation and protein expression will be determined at different locations. This will be measured in intestinal biopsies of two locations in the duodenum, in the terminal ileum, ascending colon, transverse colon and descending colon.

Study objective

Hypotheses:
- The nutrient sensing receptors have a different spatial distribution along the intestinal tract.
- The receptors: T1R2/T1R3, SGLT-1, G-protein coupled receptor 120, T1R1/T1R3, Pept1, G-protein coupled receptor 93, calcium sensing receptor, G-protein coupled receptor C6A, G-protein coupled receptor 119, cannabinoid receptor 1, CCK-1 receptor and GLP-1 receptor are expected to be located along the intestine.
- The receptors: T1R2/T1R3, SGLT-1, G-protein coupled receptor 120, T1R1/T1R3, Pept1, G-protein coupled receptor 93, calcium sensing receptor, G-protein coupled receptor C6A and G-protein coupled receptor 119 are expected to be located on the enteroendocrine cells.
- Cannabinoid receptor 1, CCK-1 receptor and GLP-1 receptor are expected to be located on the vagal nerve endings.

Study design

This study is designed as an observational study with invasive measurements

Study burden and risks

All patients undergo gastroduodenoscopy or colonoscopy for a medical reason. Only difference with regular procedure is taking 6 or 12 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 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 (12) 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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion criteria for 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)
2) Based on medical history and previous examination, no objection arises for taking extra biopsies during the gastroduodenoscopy.;- 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.;Inclusion criteria for ileal and colon biopsies:
- Step 1 (patients asked for participation):
1) Patients (male and female between 18 and 65 years) referred for colonoscopy (because of screening for colorectal cancer or follow up of colonic polyps)
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)
1) Patients with no relevant endoscopic abnormalities (colonoscopy): patients without ileal and/or colonic ulcers/polyps/diverticula and lesions suspect for malignancy

Exclusion criteria

Exclusion criteria for duodenal, ileal and colon biopsies:
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:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2012
Enrollment:	50
Type:	Anticipated

Ethics review

Approved WMO

Date:	26-03-2012
Application type:	First submission
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	NL39168.068.12