Sensing and signalling in the upper gastrointestinal tract

Impact

With the studies presented in this thesis, we aimed to understand the role of the gastrointestinal (GI) tract in preserving GI physiology by sensing the content of the gut lumen. The GI tract is a sensory organ that responds to a wide variety of signals from the GI lumen. At first, the GI tracts detects, senses and absorbs nutrients from the lumen. Second, the GI tracts senses potential noxious or toxic materials which can enter the systemic compartment via the epithelial barrier. This 'sensing and signalling' mechanism via the mucosal receptors and the intestinal network is crucial for maintaining GI homeostasis.

In the first part of this thesis we focus on the function of the GI tract and its ability to influence food intake and satiety by the detection, digestion and absorption of nutrients. The GI tract is seen as an interesting target to influence food intake and satiety. The worldwide prevalence of overweight and obesity has nearly tripled the last 40 years, which comes with increased comorbidities, such as cardiovascular diseases. Moreover, this increasing prevalence also has significant economic and social impact. Bariatric procedures are successful in inducing weight loss on the long term in morbidly obese patients. However, patients with overweight are not eligible for these procedures. Therefore, non-invasive novel strategies are needed in the battle against the obesity epidemic. This thesis provides two studies in which macronutrients (lipid, carbohydrates and protein) were encapsulated and ingestion of these products resulted in a decrease in food intake. Future studies should focus on whether this effect is also observed after repetitive or chronic ingestion of these products. However, these studies provide a first step towards the development of novel functional foods. Encapsulated nutrients targeting the distal small intestine can be added in a dairy product in order to increase satiety and reduce food intake. This strategy could be of benefit in overweight patients or to prevent overweight to occur in normal weight patients.

Both the stomach and the small intestine have an important role in controlling food intake and satiety, but underlying mechanisms differ from each other. The satiating effect from the stomach mainly occurs via stretching and tension mechanoreceptors after ingestion of a meal. In this thesis, we investigated whether this effect could be influenced by the infusion of lidocaine, a local anaesthic, in the stomach via a nasogastric catheter. We observed that infusion of lidocaine resulted in a small, but non-significant increase in food intake. However, we cannot exclude that the intubation may have influenced the results observed in our study. Future studies

need to consider other methods of administration of the lidocaine into the stomach, for example encapsulation, in order to further investigate the effect of lidocaine on the mechanoreceptors in the stomach wall. Moreover, strategies to target the entire stomach wall should also be considered.

Besides nutrients, other food components are sensed by the GI lumen. This thesis investigated the potential role of the non-caloric bitter substance in decreasing food intake and increasing satiety. Tastants can serve as an important nutritional target in the treatment of overweight and obesity. However, the decrease in food intake observed was rather small. The impact of this study is in line with the studies in which macronutrients were encapsulated; a rather modest effect on food intake. However, ingestion of a certain amount of capsules with the bitter substance could lead to a reduction in food intake and subsequently in a reduction in body weight. Future, long-term studies are needed to investigate whether this strategy can be preventive in the battle against overweight and obesity.

In the second part of this thesis focused on the responses of the upper GI tract and the role of TRPV1 against potential noxious substances. We observed that infusion of capsaicin, the pungent substance of chilli peppers, into the distal esophagus resulted in pain and a decrease in impedance of the esophagus wall. This was also related to the intercellular space area in the distal esophagus. This suggests that an impaired mucosal barrier plays a major role in pain symptom generation in patients with non-erosive reflux disease (NERD). This study provides additional insight into esophageal pain symptom generation which has clinical relevance for treatment of heartburn and related symptoms, providing additional rationale for esophageal barrier protection as a therapeutic modality. The findings in this study can open the scientific discussion in order to establish the position of mucoprotective agents in the management of reflux symptoms. Future studies should focus on which structural aspects of these mucoprotective compounds are responsible for the beneficial effect.

In summary, the research presented in this thesis shows that the upper GI tract has an important role in maintaining gut-health and that it can be considered as an interesting target to influence GI psychology in a beneficial way. Sensing of nutrients and food components in the upper GI tract can be seen as an interesting target to influence food intake and satiety. Moreover, the epithelial barrier in the upper GI tract is considered to play a major role in the protection against potential noxious substances. Taken together, this thesis provides relevant information regarding the

sensing and signalling function of the upper GI tract in order to activate several pathways that are involved in maintaining GI and systemic homeostasis.