

Novel strategies to address disrupted sensing and signalling of satiety

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Impact

Since 1975, the prevalence of obesity in the population has nearly tripled. Obesity and overweight pose an evident burden and are linked to the occurrence of several diseases such as diabetes mellitus and cardiovascular diseases. Currently, only surgical options are an effective strategy for long-term weight loss. However, surgical treatment is invasive and only available for a selected group of morbidly obese subjects. Therefore, novel non-invasive treatment and preventive strategies are needed to battle the obesity epidemic. On the other hand, decreased food intake and increased satiety feelings are frequently seen in the aging population. A possible explanation could be altered sensitivity of pressure and nutrient and taste sensors in the stomach and small bowel. The gastrointestinal tract plays an important role in regulating food intake behaviour via release of gut peptides. Therefore, food-gut interactions could provide us with a strategy to influence and manipulate food intake behaviour.

The signalling of appetite can also be disrupted by abnormal sensations such as stress, anxiety, and recurrent pain. This can result in avoidance of food intake. Functional dyspepsia is a disorder in which patients experience symptoms such as bothersome early satiation, postprandial fullness, epigastric pain, and/or epigastric burning. However, no evidence for systemic, metabolic, or organic diseases can be found that is able to explain these symptoms. The presence of these symptoms is already sufficient to result in avoiding further food intake.

The aim of this thesis was to provide an in-depth understanding of interactions between food and the gastrointestinal tract related to satiety and eating behaviour. Hereby, we aimed to provide leads and thereafter develop and optimise therapeutic and preventive strategies that can correct disturbed (*i.e.*, too high or too low) energy intake. Moreover, this thesis described the validation and application of a novel tool that will provide more insight into the disturbed sensing and signalling of appetite as observed in patients with functional dyspepsia.

This thesis highlighted the potential role of non-caloric bitter substances in decreasing food intake. However, this decrease in food intake is rather modest. Appetite signalling in obese individuals is substantially dysregulated. Therefore, the place of bitter substances in battling the obesity epidemic should be more as a preventive strategy, rather than a treatment strategy. This is also in line with the current concept of shifting the focus in healthcare from therapeutic care and cure towards prevention. In this thesis the scientific steps that need to be undertaken before implementing this preventive strategy were

provided. The most important step is harmonising the designs of studies conducted by different research groups in order to generate more consistent data.

An intriguing observation in this thesis was that that local application of lidocaine, a local anaesthetic, in the stomach in humans was able to modify food intake although the overall effect was not statistically significant. However, in order to apply lidocaine a rather invasive method was used. We cannot exclude that the intubation negatively influenced the study results. Therefore, we advise future studies to consider other methods of administration of lidocaine in the stomach in order to further substantiate this concept.

Additional studies in this thesis investigated the usefulness of a novel assessment method for patients with functional dyspepsia. In these studies, we demonstrated the ability of this assessment method to capture the same constructs as conventional questionnaires. Moreover, we demonstrated the ability of the new assessment method to characterise individual symptom patterns. This provides us with a tool that can help move towards a more personalised approach in treating this functional symptom-based disorder. Using this novel tool, patients will be able to develop disease insight, shared-decision making can be improved, and patients can be provided with tools for self-management of their disease.

In summary, the first part of this thesis focused on generating knowledge on a strategy that has the potential to prevent the expansion of the obesity epidemic. Second, the first in-human experiment investigating a novel treatment tool for individuals with reduced food intake has been described. This paves the way for research to further elucidate the concept of modifying gastrointestinal responses to specific luminal triggers to influence satiety signalling and eating behaviour. Third, a novel tool that can aid functional dyspepsia patients in the transition towards personalised health care has been evaluated and was validated. Overall, this thesis, therefore, provided novel strategies to address disrupted sensing and signalling of satiety and eating behaviour.