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Identification of nutrient-specific receptors in the intestine and their role in signaling

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SUMMARY

Overweight, obesity and the associated diseases like diabetes, cardiovascular diseases or even certain cancers are a growing problem in all developed and developing countries. Morbidity, mortality and socio-economic costs arising from this global healthcare problem are considerable. Obesity is the expression of the imbalance between energy intake and energy expenditure. One key question is: what causes the high energy intake in humans and how does this relate to the mechanisms involved in appetite regulation and satiety signaling. The gastrointestinal tract is central in the context of satiety control. It acts as a sensor for both the quantity and quality of the foods ingested, secreting hormones that can induce hunger (orexigenic signals) and transmitting anorexigenic signals to the brain and peripheral tissues to induce satiety and prepare the organs for the incoming nutrients and energy. These hormones, secreted from endocrine cells embedded into the gastrointestinal epithelium, are now recognized to play a fundamental role in these physiological processes. *In vitro* studies with enteroendocrine cell lines and studies in rodent models have identified numerous nutrient sensing pathways in the gastrointestinal (GI) tract leading to hormone secretion that can also affect satiety. Clinical studies in humans have shown that GI hormone infusion (PYY, GLP-1 analogs, CCK) decreases appetite and increases the satiety feeling in volunteers, thus contributing to reduce the overall meal size and food intake. The signaling pathways underlying the gut-brain communication remain however largely elusive, and this is particularly true for the intestinal sensors involved in the first steps of this feeding regulation. The present thesis aimed to identify and characterize novel nutrient-sensing pathways leading to hormone secretion in the intestine. Therefore, established enteroendocrine models were used in combination with newly adapted *ex vivo* models to assess initial events involved in chemo-sensation in the intestinal mucosa. We thus identified and characterized two novel nutrient-sensing pathways in human enteroendocrine cells, using a combination of physiological and molecular tools. These original data address a new sensing pathway selective for tetrapeptides found in a human enteroendocrine cell model secreting GLP-1, and a novel bitter receptor-mediated secretion of CCK in human enteroendocrine cells also demonstrated in a *ex vivo* rat intestinal model. These findings may hopefully foster additional research in the field of nutrient-sensing, particularly concerning the role of taste receptors present in the intestine and leading to hormone secretion that affect satiety.

Keywords: nutrient sensing; satiety; enteroendocrine cells; taste receptors; GLP-1; CCK