1 Summary

Over the past decades, significant progress has been made in understanding appetite regulation revealing a complex interplay between the central nervous system and the organs in the periphery involved in energy homeostasis. The discovery of gut released peptides and their role in controlling food intake has gradually put the gastrointestinal tract in the spotlight and research in the role of the so-called “gut-brain axis” in the control of food intake is receiving increased attention. The vagus nerve is emerging to play an essential role in this gut-brain communication.

Fat is an energy-dense macronutrient and upon digestion stimulates the secretion of a repertoire of gut peptides. The major component of dietary fat is triacylglycerol, which in the gut lumen hydrolyses into fatty acids and 2-monoacylglycerol. The two digestion derivatives are ligands for different G protein-coupled receptors in the gut and stimulate a set of signals that includes cholecystokinin (CCK) and glucagon-like peptide 1 secretion (GLP-1). In this dissertation, we aimed to delineate the physiological mechanisms in the gastrointestinal regulation of fat intake and the role of the vagus nerve in the signalling of fat-induced satiation, with emphasis on the gut-derived CCK and GLP-1.

To dissociate oral fat intake preferences and focus on post-oral gut mechanisms, we employed an intragastric fat self-administration mouse model, where mice with implanted gastric catheters were trained to self-infuse fat emulsions and self-regulate their intake. Additionally, to evaluate the involvement of the CCK receptor-expressing neurones of the vagus nerve in fat-induced satiation, we performed bilateral nodose ganglia injections with saporin-CCK conjugates. This model was employed alone or combined with the fat self-administration model in our studies.

CCK is a well-described endogenous satiation signal, whereas the role of endogenous GLP-1 in the control of food intake is still unclear. In **manuscript I**, we demonstrate that CCK and GLP-1 plasma levels increase following voluntary post-oral fat intake and that endogenous CCK and GLP-1 are important for fat-induced satiation.

In addition, our data indicate that endogenous CCK and GLP-1 act together to inhibit post-oral fat intake further.

Intraperitoneally injected GLP-1 is known to inhibit food intake, although this effect seems to depend on the nutritional status of the animal with the effect being observed only at the fed state. In **manuscript II**, we hypothesised that other gut peptides released during a meal might influence the subsequent effect of intraperitoneal GLP-1, and investigated whether CCK provides such a signal. We found that activation of the free fatty acid 1 receptor (FFA1) with TAK875 increases plasma CCK levels and that prior activation of the FFA1 receptor increases the anorectic effect of GLP-1. In addition, ablation of the vagal CCK receptor-expressing afferents attenuated the combined anorectic effect of TAK875 and GLP-1. These data further substantiate the interaction of CCK and GLP-1 in fat-induced satiation and are suggestive of the interactions occurring at the level of the vagus nerve. Finally, we investigated the post-oral responses of mice, with lesioned vagal CCK receptor-expressing neurones to fat and linoleic acid. The results indicate that vagal lesioning results in fat sensing deficiency and increased post-oral fat intake. More importantly, substantial impairment of linoleic acid-sensing was observed, demonstrating an essential role for the CCK receptor-expressing vagal afferent neurones for long-chain fatty acid signalling in the regulation of post-oral fat intake.