Obesity is a common metabolic condition that is becoming more prevalent globally, but current treatments have limitations. Prolactin-releasing peptide (PrRP), a neuropeptide that reduces food intake after administration to the third ventricle, loses this ability when administered peripherally. However, lipidization of peptides enhances their stability in the bloodstream and facilitates their central effect after peripheral administration. We developed lipidized analogs of PrRP, which have high potential as a treatment option for obesity. We previously demonstrated that peripheral administration of lipidized PrRP analogs led to a substantial reduction in food intake and body weight in mice, with palm-PrRP31 and palm^{11}-PrRP31 emerging as key analogs. In this study, we aimed to further investigate the mechanisms underlying the effects of these two PrRP31 analogs *in vitro*.

Natural PrRP31 binds to its receptor GPR10 and with high affinity to neuropeptide FF receptor type 2 (NPFFR2), which are both expressed in regions involved in food intake regulation. The palmitoylation of PrRP31 increased their binding and agonist properties for both GPR10 and NPFFR2 receptors. Lipidized analogs exhibited a stronger affinity also for another neuropeptide FF receptor, NPFFR1, suggesting that NPFFR1 could be a new potential target for PrRP31 analogs. The molecular mechanisms underlying the effects of palmitoylated PrRP31 analogs on cellular signaling pathways were studied in cells expressing GPR10, NPFFR2, and NPFFR1. Palmitoylated PrRP31 analogs stimulated the activation of multiple signaling kinases such as MAPK, Akt, and CREB, and transcription factors c-Foc and c-Jun, which are involved in regulation of various cellular processes such as cell cycle progression, migration, and differentiation.

The second part of the thesis was focused on *in vivo* experiments involving metabolic phenotyping of NPFFR2-deficient and GPR10/NPFFR2-deficient mice, fed either standard or high-fat diets, and comparing them to age-matched control mice. We observed that deficiency of NPFFR2 resulted in glucose intolerance impaired on a high-fat diet. Moreover, NPFFR2 knock-out mice showed a disrupted central PI3K/Akt signaling pathway. Deletion of both GPR10 and NPFFR2 receptors resulted in sex-specific and diet-dependent changes leading to prediabetic symptoms. When fed a high-fat diet, both sexes exhibited hyperinsulinemia. Moreover, female GPR10/NPFFR2-deficient mice also showed impaired glucose tolerance and hyperglycemia when fed high-fat diet.