ABSTRACT

The increasing number of overweight and obese individuals has become a major health issue in our society. The etiology of obesity often involves excessive hyperphagia, highlighting the importance of comprehensive understanding the regulation of food intake regulation in order to effectively treat this chronic condition. Ghrelin, a peripheral peptide hormone responsible for increasing food intake, directly affects the hypothalamus through the growth hormone secretagogue receptor (GHSR). Recently, it was found that liver expressed antimicrobial peptide 2 (LEAP2) naturally counteracts the effects of the GHSR as an inverse agonist. This makes LEAP2 a potential candidate for the development of anti-obesity treatment.

This thesis explores the interaction between ghrelin and LEAP2 in the context of food intake regulation and obesity. Firstly, it focuses on modified N-terminal peptide LEAP2(1-14) and its lipidized analogs, examining their affinity to and activation of GHSR *in vitro* and *in vivo*. The results demonstrate that palmitoylated LEAP2(1-14) (palm-LEAP2(1-14)) exhibits the most pronounced affinity for GHSR, acts as GHSR inverse agonist, reduces food intake, inhibits growth hormone release, and shows increased stability in rat plasma. These findings suggest that palm-LEAP2(1-14) holds promise as an anti-obesity treatment.

Furthermore, the study investigates the impact of a high-fat (HF) diet on obesity and the development of ghrelin and LEAP2 resistance in mice. The results reveal that HF diet feeding decreases active and total plasma ghrelin, increases liver *LEAP2* mRNA expression, and leads to glucose intolerance. The switch to a standard diet normalizes liver *LEAP2* mRNA expression and active ghrelin levels but not total ghrelin. Furthermore, the study demonstrates resistance to palm-LEAP2(1-14) induced by the HF diet and also resistance to GHSR stable agonist [Dpr^3]Ghrelin, which is reversible upon switching to a standard diet.

Lastly, the potential of palm-LEAP2(1-14) to counteract the effects of a HF diet on body weight gain and normalize morphometric and metabolic parameters associated with obesity was evaluated. Palm-LEAP2(1-14) slightly reduced the body weight gain induced by HF diet feeding and decreased plasma leptin level. But overall, palm-LEAP2(1-14) was not able to suppress the effect of HF diet due to palm-LEAP2(1-14) resistance.

These findings advance our comprehension of obesity pathophysiology and indicate the necessity for additional investigation into alternative approaches to improve the efficiency of anti-obesity treatments that target the ghrelin and LEAP2 pathways.