ABSTRACT

The thesis is focused on the effect of ghrelin receptor (GHS-R1a) agonists and antagonist on food intake regulation. Ghrelin is the only known periferally produced orexigenic hormone and the only known acylated hormone. GHS-R1a agonists and antagonists could be useful in the treatment of cachexia and obesity, respectively.

In the first part of the thesis, newly designed peptidic GHS-R1a agonists were characterized. The agonists were stabilized by replacing octanoylated Ser^3 with a fatty acid coupled to diaminopropionic acid by a stable amide bond. Other noncoded amino acids were also incorporated. Ghrelin analogs were modified by replacing the octanoyl group with another fatty acid, incorporation of the second fatty acid or shortening the peptide chain. Most of the tested GHS-R1a agonists were found to possess high affinities for GHS-R1a ($K_i = 10^{-9}$-10^{-10} nM) and to activate signaling pathways of ghrelin. After subcutaneous (SC) administration to mice, agonists showed significant and prolonged orexigenic effect.

In the second part of the thesis, acute and long-term effects of pseudopeptide GHS-R1a agonist JMV1843 were tested in lean C57BL/6 mice. Acute SC administration of JMV1843 to fed mice increased food intake in a dose-dependent manner (ED_{50} = 1.94 mg/kg). JMV1843 was stable in blood serum *in vitro* for 24 h. 10-day treatment with JMV1843 (SC administration) significantly increased food intake, body weight and mRNA expression of the orexigenic neuropeptides in the medial basal hypothalamus and decreased the expression of thermogenic uncoupling protein 1 in brown adipose tissue.

In the third part of the thesis, acute and long-term effects of nonpeptide GHS-R1a antagonists JMV3002 and JMV4208, compounds based on 1,2,4-triazole structure, were tested. Their acute SC administration decreased food intake in fasted lean mice in a dose-dependent manner (ED_{50} = 5.25 and 2.05 mg/kg). Both compounds were stable in mouse blood *in vivo*. 14-day treatment with the ghrelin antagonists decreased food intake, body weight, adipose tissue mass and expression of the lipogenesis-promoting enzymes in mice with diet-induced obesity (DIO).

Key words:

Ghrelin, GHS-R1a agonist, GHS-R1a antagonist, food intake, mice, cachexia, obesity