Ghrelin receptor ligands: from the bench to the drug on the market

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Ghrelin receptor or GHS-R1a for Growth Hormone Secretagogue Receptor type 1a is a G protein-coupled receptor (GPCR) that mediates ghrelin-induced growth hormone (GH) secretion, food intake, and reward-seeking behaviors. Because of its possible implication in several physiological disorders such as obesity and drugs/alcohol addictions, GHS-R1a represents a major target for the development of therapeutic small molecules.

We previously described a potent Growth Hormone Secretagogue (GHS), the pseudopeptide compound JMV 1843. This compound is a selective agonist of GHS-R1a able to mimick ghrelin and to act by oral route in man. Acting as a GHS, it is able to elicit a large secretion of GH which can then be dosed in the blood. It has completed its clinical phases and was approved by the FDA for GH deficiency diagnosis in aldults. This compound is commercialized by Æterna-Zentaris since 2018 under the trademark of Macrilen®. It is also in clinical phase II for the treatment of cachexia.

The implication of GHS-R1a in food intake focused the attention on ghrelin receptor antagonists for the treatment of obesity. Starting from JMV 1843, we achieved to design and prepare a series of novel small molecules, based on the 1,2,4-triazole scaffold, able to antagonize ghrelin-induced GHS-R1a signaling. This peptido-mimetic series have been investigated on one hand for their ability to compete for ghrelin binding and to activate or to inhibit calcium uptake in cells transiently expressing GHS-R1a and on the other hand for their effects on food intake and GH secretion in animal models. Our results showed that several non-peptide compounds characterized in vitro as antagonist or partial agonist of GHS- R1a inhibited food intake without altering GH secretion in vivo. We found that the dissociated effect of these ligands on food intake and GH secretion was correlated with their functional selectivity toward signaling pathways of GHS-R1a, making these ligands "biased". Thus this study supports the feasibility of a specific pharmacological modulation of the ghrelin effect on appetite. The preclinical results obtained with some of our best compounds (such as JMV 2959) will be presented.

As GHS-R1a displays a very high constitutive activity (more than 50% of its maximal activity) it is thought that inverse agonists could potentially decrease food intake and body weight. Starting from JMV 2959, we recently developed a series of inverse agonists based on our 1,2,4-triazole scaffold. In vitro results of these compounds will be presented.

Finally, the recent development concerning LEAP2 (Liver-Expressed Antimicrobial Peptide 2) biological activities toward GHS-R1a will be reported.