Design and functional profiling of new KISS1R agonists

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The discovery of the kisspeptin (Kp)/KISS1R system represented a major breakthrough in the understanding of the mechanisms underpinning the control of reproduction. Kisspeptins are derived from a precursor that is processed to produce smaller peptides that, based on their amino acid sequence length, were named Kp54, Kp16, Kp14, Kp13, and Kp10. All these peptides are capable of activating with high potency their cognate receptor, KISS1R. Kp10 is capable of inducing a sharp increase of plasma LH and FSH concentration in human, rodents and livestock through the activation of GnRH neurons. Furthermore Kp10, when continuously infused in anoestrus ewe, is capable of inducing an ovulatory cycle. However, endogenous Kp isoforms have an extremely short *in vivo* half-life and are rapidly cleared by the kidney. Hence they are not suitable for applications requiring a prolonged activity such as that necessary for treating some pathological conditions or to induce ovulation. In order to circumvent this problem we decided to synthesize, starting from the Kp10 scaffold, a series of analogs resistant to degradation and with reduced renal clearance. Several protease cleavage sites have been identified in the Kp10 sequence. By systematically modifying these cleavage sites we created analogs with improved stability in the blood but also increased potency. Furthermore to tackle the problem of renal clearance we increased the affinity of the analogs for serum albumin by conjugating them with an albumin binding molecule. Preliminary *in vivo* data in ewe indicate that these new analogs induce an increase of LH plasma concentration that is stronger and longer-lasting than that triggered by Kp10. These results suggest that our analogs have a potential to treat various human reproductive disorders resulting from a reduced activity of the hypothalamus-pituitary axis and to improve the management of livestock reproduction.

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