ENDOCRINE AND EXTRAENDOCRINE EFFECTS OF GHRELIN AND NOVEL SYNTHETIC ANALOGS

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Growth Hormone Secretagogues (GHS) are synthetic molecules endowed with strong GH-releasing activity both *in vitro* and *in vivo* in several animal species, including humans. They mimic the endogenous hormone ghrelin, a peptide of 28 aa synthesized predominantly by the stomach and gastrointestinal tract, which exerts its biological actions by binding to the GHS-R1a, a G-protein coupled receptor. Beside the endocrine properties, ghrelin and the GHS show also extraendocrine activities, including an orexigenic effect. It is known that the GH-releasing activity of ghrelin is mediated by GHS-R1a; however, it is not yet unequivocally established whether the GHS-R1a is involved also in the orexigenic effect of some GHS. Thus, the aim of our research is to determine whether binding to the GHS-R1a could be predictive of the orexigenic or anorexigenic activity of novel ghrelin analogs. To this goal, an immortalizated Chinese Hamster Ovarian (CHO) cell line was stably transfected with the human GHS-R1a and fluorescence changes produced by increased intracellular Ca^{2+} levels were measured as an index of receptor activation. Using this model, the properties of ghrelin and of three GHS (JMV2760, JMV-2844 and JMV-2951) have been characterized. The results demonstrate that all the compounds, with the exception of JMV-2844, activate *in vitro* the GHS-R1a. Next, the endocrine activity of these molecules has been studied, by investigating their ability to stimulate the GH release in infant rats, a model particularly responsive to GH-releasing stimuli. Ghrelin and hexarelin effectively stimulated GH secretion, JMV-2951 possesses a weak GH-releasing activity, whereas JMV2760, and JMV-2844 were inactive. Moreover, JMV2760 were able to significantly inhibit the GH release induced by hexarelin. At last, we investigated the ability of JMV2760, JMV-2844 and JMV-2951 to affect food intake in the young-adult rat. Ghrelin, hexarelin and JMV-2951 effectively stimulated food consumption in satiated rats, whereas JMV2760 and JMV-2844 were inactive *per se* but significantly inhibited the orexigenic effect of hexarelin.
In conclusion, our results demonstrate that the ability of GHS to activate *in vitro* the GHS-R1a is not predictive of their biological activity *in vivo* and that the endocrine and extraendocrine effects could be mediated also by receptors different from the GHS-R1a.