Targeted Nanoparticles Towards Increased L Cell Stimulation As A Strategy To Improve Oral Peptide Delivery In Incretin-based Diabetes Treatment

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Abstract

Introduction: The delivery of therapeutic peptides via the oral route remains one of biggest challenges in the pharmaceutical industry. Recently, we have described an alternative improved drug delivery system for the oral delivery of peptides, consisting on a lipid-based nanocapsule (1,2). We have developed an innovative dual-action approach that synergizes the biological effect of the nanocarriers (inducing endogenous GLP-1 secretion) with that of the encapsulated molecule (increased absorption of the encapsulated peptide).

Methods: We have developed and compared different fatty acid-targeted lipid and polymeric nanoparticles to strengthen the nanocarriers' GLP-1 secretory effect and/or prolong their antidiabetic effect *in vivo*. To that purpose, we evaluated the L cell stimulation induced by the nanocarriers both *in vitro* in murine L cells, and *in vivo* in normoglycemic mice. We further examined their antidiabetic effect *in vivo* in a high fat diet-induced obese/diabetic mouse model, examining the effect of the oral administration frequency.

Results: Among the tested nanocarriers, only lipid-based nanocarriers modified with DSPE-PEG_{2000}-CH_3 on the surface were able to significantly strengthen the biological effect of the nanocarriers. They were able to increase endogenous GLP-1 levels up to 8-fold *in vivo* in normoglycemic mice. Moreover, they were effective at prolonging the *in vivo* antidiabetic effect normalizing plasma glucose levels in obese/diabetic mice following a long-term treatment (one month). Ultimately, the targeted nanocarriers were as effective when reducing the administration frequency from once daily to once every other day.

Conclusion/Implications: In conclusion, we increased the endogenous secretion of GLP-1 and prolonged the antidiabetic effect of our formulation by modifying the surface of our nanocarriers.

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References: (1) Xu Y. et al. Mol Pharm. 2018 (15):108-115. (2) Xu Y. et al. Gut. 2019, in press.

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Learning Objectives:

- To develop targeting strategies to strengthen the endogenous secretion of GLP-1 induced by nanocarriers
- To evaluate the antidiabetic efficacy of our formulation in an obese/diabetic model
- To evaluate the prolonged effect of our formulation reducing the frequency of administration