Acylation of salmon calcitonin modulates in vitro intestinal peptide flux through membrane permeability enhancement - DTU Orbit (08/11/2017)

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Acylation of peptide drugs with fatty acid chains has proven beneficial for prolonging systemic circulation, as well as increasing enzymatic stability and interactions with lipid cell membranes. Thus, acylation offers several potential benefits for oral delivery of therapeutic peptides, and we hypothesize that tailoring the acylation may be used to optimize intestinal translocation. This work aims to characterize acylated analogues of the therapeutic peptide salmon calcitonin (sCT), which lowers blood calcium, by systematically increasing acyl chain length at two positions, in order to elucidate its influence on intestinal cell translocation and membrane interaction. We find that acylation drastically increases in vitro intestinal peptide flux and confers a transient permeability enhancing effect on the cell layer. The analogues permeabilize model lipid membranes, indicating that the effect is due to a solubilization of the cell membrane, similar to transcellular oral permeation enhancers. The effect is dependent on pH, with larger effect at lower pH, and is impacted by acylation chain length and position. Compared to the unacylated peptide backbone, N-terminal acylation with a short chain provides 6- or 9-fold increase in peptide translocation at pH 7.4 and 5.5, respectively. Prolonging the chain length appears to hamper translocation, possibly due to self-association or aggregation, although the long chain acylated analogues remain superior to the unacylated peptide. For K(18)-acylation a short chain provides a moderate improvement, whereas medium and long chain analogues are highly efficient, with a 12-fold increase in permeability compared to the unacylated peptide backbone, on par with currently employed oral permeation enhancers. For K^{18}-acylation the medium chain acylation appears to be optimal, as elongating the chain causes greater binding to the cell membrane but similar permeability, and we speculate that increasing the chain length further may decrease the permeability. In conclusion, acylated sCT acts as its own in vitro intestinal permeation enhancer, with reversible effects on Caco-2 cells, indicating that acylation of sCT may represent a promising tool to increase intestinal permeability without adding oral permeation enhancers.

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