Hanne Mørck Nielsen[1,*], Mie Kristensen[2], Ditlev Birch[1], Sofie Fogh Hedegaard[1], Henrik Franzyk[3]

[*]Presenting author
[1]Center for Biopharmaceuticals and Biobarriers in Drug Delivery
[2]CNS Drug Delivery & Barrier Modelling, [3]Natural Products and Peptides
All: University of Copenhagen, Copenhagen, Denmark

hanne.morck@sund.ku.dk

Conjugation to cell-penetrating peptides influences their membrane interaction and safety

Therapeutic peptide and protein drug entities are of high therapeutic relevance due to their potency and specific mode of action. A major obstacle for the successful delivery of peptide/protein drugs to their target site is their poor transport across biological membranes. This renders that administration is to a large extent done by injection, which is often experienced as inconvenient for the patients. Oral administration may, however, be pursued for some peptide molecules if pharmacologically relevant. Sufficient delivery of peptide drugs via the gastrointestinal tract is, however, limited both by their poor enzymatic stability and their large molecular size, the latter hindering non-aided permeation across the intestinal epithelium.

A class of membrane-interacting peptides, cell-penetrating peptides (CPPs), has demonstrated promising potential as carriers for delivery of therapeutic cargoes across biological membranes. To enhance the transmembrane delivery of a cargo peptide like the parathyroid hormone fragment 1-34 by using CPPs, conjugates of the therapeutic cargo with the CPP molecule has been pursued. The mechanism by which CPPs interact with biological membranes and act as carriers for transmembrane delivery of a conjugated cargo is heavily debated but known to depend on the molecular properties of the CPP. Numerous studies seek to elucidate the mechanism of membrane interaction of the CPPs by applying a range of techniques involving conjugation of fluorophores to the CPP.

Conjugation of a therapeutic molecule or a fluorophore to CPPs inevitably will change the physicochemical properties of the CPP. This fact likely influences the degree and mechanism of membrane interaction, affect delivery efficiency, and potentially lead to undesired cellular effects [1]. We here report on the importance of molecular properties of CPP conjugates in relation to their effect on biological membranes employing studies on lipid bilayers as well as cell culture models.

Figures

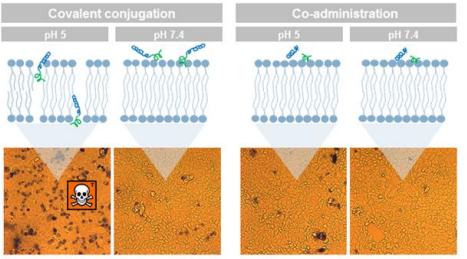

Figure 1: Conjugation of a cell-penetrating peptide, penetratin, to parathyroid hormone 1-34 alters the mode and degree of interaction with epithelial cells compromising safety [2].

References

[1] Birch, D, Christensen, MV, Staerk, D, Franzyk, H, Nielsen, HM. BBA-Biomembranes, 1859 (2017) 2483-2494.

[2] Kristensen, M, Nielsen, LH, Zór, K, Boisen, A, Christensen, MV, Berthelsen, J, Nielsen, HM, Bioconjugate Chem. (2018) *in press*.