Enhancer-driven changes in Peptide Permeability on *In Vitro* models

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Introduction

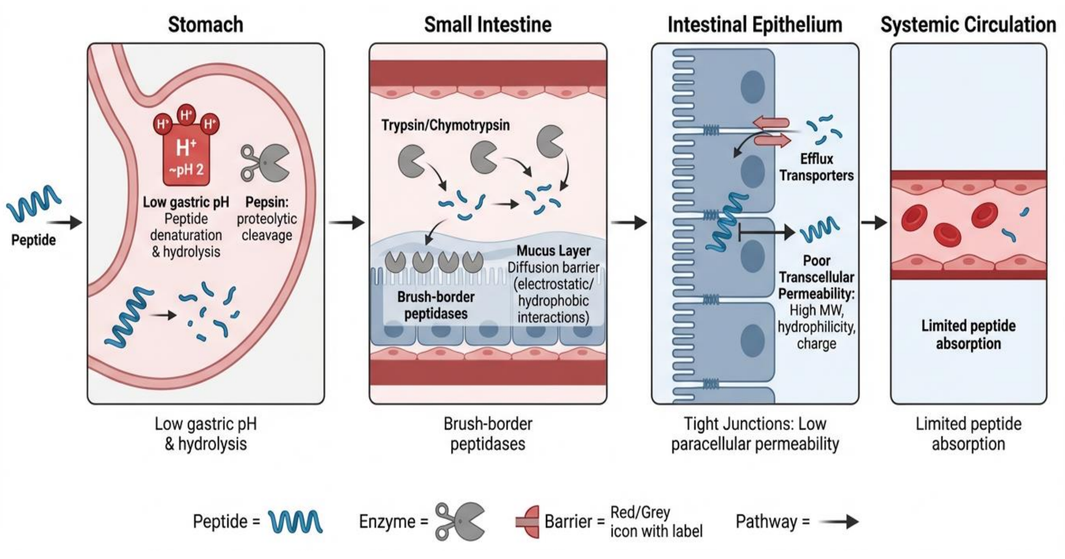
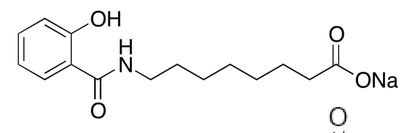
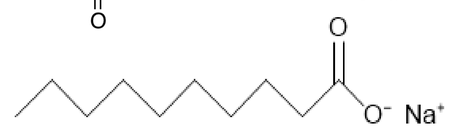


Figure 1. Overview of physicochemical barriers affecting the oral absorption of peptide therapeutics in the human GI tract

- The development of oral peptide therapeutics is significantly impacted by poor permeability through the gastrointestinal (GI) epithelium, as well as by enzymatic degradation - finally resulting in low peptide absorption and low bioavailability
- Permeation enhancers SNAC (salcaprozate sodium) and C10 (sodium caprate) are used in advanced oral peptide formulations to fix low peptide's GI absoption
- SNAC



- C10



- Accurate assessment of peptide's *in vitro* apparent permeability considered essential for identifying viable drug candidates

Key challenges

- **Low intestinal permeability**
  large size and high polarity of peptides results in poor oral absorption
- **Poor recovery and non-specific binding**
  Adsorption to assay components can lead to significant loss and inaccurate estimates (poor *in vitro to in vivo* correlation)
- **Enzymatic instability**
  Rapid degradation by intestinal and cellular proteases complicates interpretation of transport data

Aim

Systematically evaluate how C10 and SNAC modulate permeability and recovery of a panel of linear and cyclic peptides across *in vitro* epithelial cell models

Methods

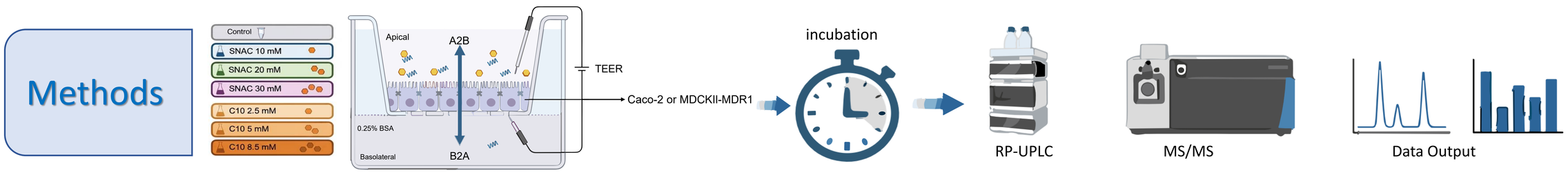


Figure 2. Schematic representation of the *in vitro* epithelial barrier model and experimental workflow

Results

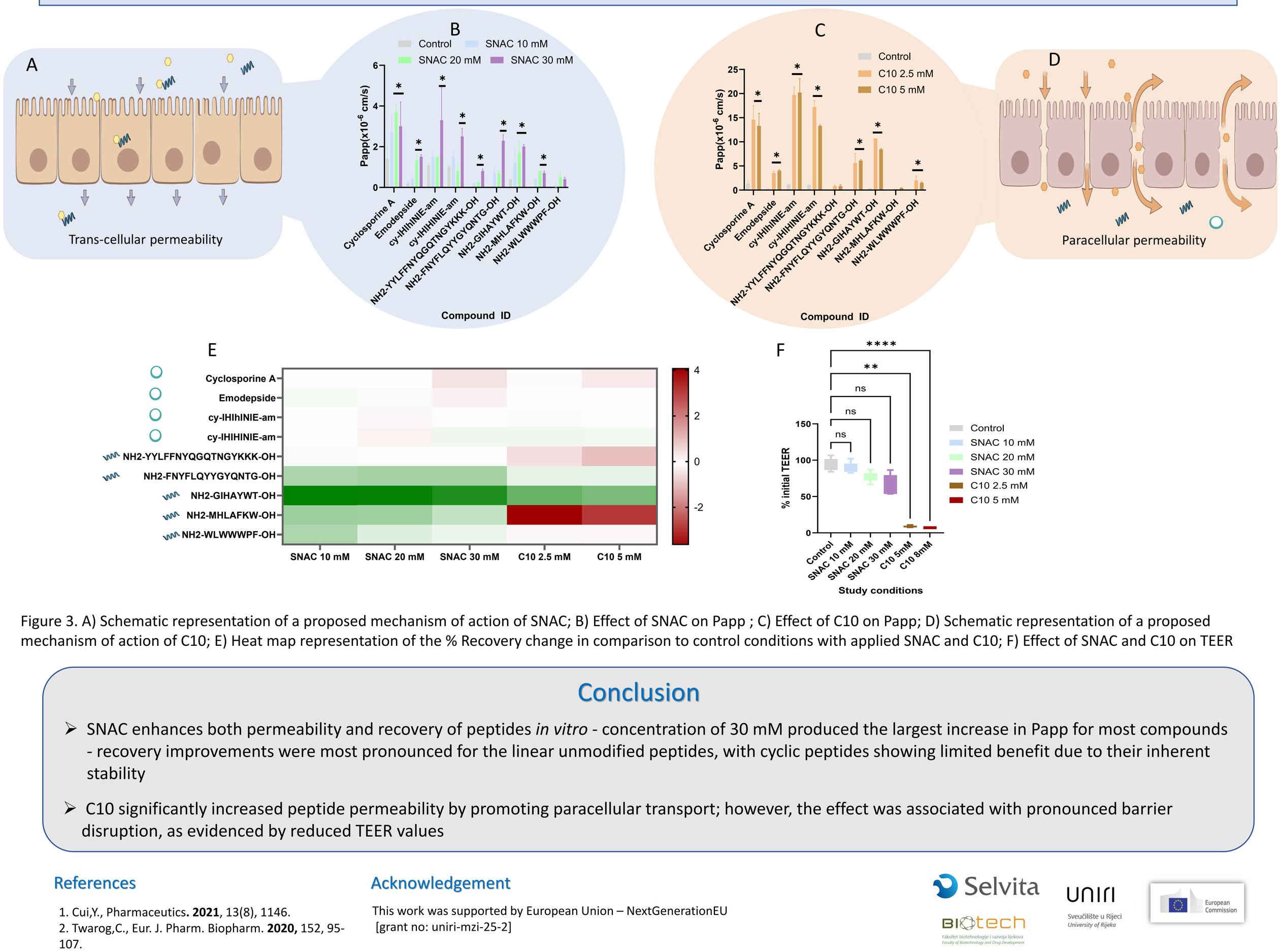


Figure 3. A) Schematic representation of a proposed mechanism of action of SNAC; B) Effect of SNAC on Papp ; C) Effect of C10 on Papp; D) Schematic representation of a proposed mechanism of action of C10; E) Heat map representation of the % Recovery change in comparison to control conditions with applied SNAC and C10; F) Effect of SNAC and C10 on TEER

Conclusion

- SNAC enhances both permeability and recovery of peptides *in vitro* - concentration of 30 mM produced the largest increase in Papp for most compounds - recovery improvements were most pronounced for the linear unmodified peptides, with cyclic peptides showing limited benefit due to their inherent stability
- C10 significantly increased peptide permeability by promoting paracellular transport; however, the effect was associated with pronounced barrier disruption, as evidenced by reduced TEER values

References

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Acknowledgement

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