OPINION

Cyclosporin is a lipophilic cyclic peptide that form gels to clump together

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ABSTRACT

Cyclic peptides are promising prospects for orally administered medicines, but limited intestinal permeability has hampered their development. Although certain biological mechanisms that affect cyclic peptide intestinal permeability have been identified, the impact of the mucus barrier, a key stumbling block to epithelial medication delivery, on cyclic peptide bioavailability remains unknown. We show that the lipophilic cyclic peptide cyclosporin A (CsA) interacted with polymeric, gel-forming mucins (MUC2, MUC5AC, and MUC5B), which support the mucus gel-networks in the gastrointestinal tract, and likely caused aggregation. Two additional cyclic peptides (daptomycin and polymyxin B) did not produce mucin aggregation under the same circumstances. Purified MUC2, MUC5AC, and MUC5B mucins sedimented quicker in the presence of CsA using rate-zonal centrifugation, with a substantial increase in mucins in the pellet fraction. Mucin sedimentation patterns, on the other hand, were substantially unaffected by daptomycin or polymyxin B therapy. CsA promoted MUC5B sedimentation in a concentration-dependent manner, and sedimentation tests using recombinant mucin protein domains indicate that CsA is most likely responsible for aggregation of MUC5B's largely non-O-glycosylated N-terminal and C-terminal regions. Furthermore, pH influenced the aggregation of the N-terminal area but not the C-terminal region.

INTRODUCTION

The CsA possesses partly N-methylated amide groups; this unusual chemical structure, which is not found in dapt--mycin or polymyxin B, might play a role in its interaction with gel-forming mucin. Our findings suggest that under healthy settings, the interaction of gel-forming mucins with the cyclic peptide CsA is mediated at the N- and C-terminal domains of mucin polymers. The mucus barrier is a key physiological component that regulates cyclic peptide intestinal penetration in vivo, according to our results. Proteins, peptides, nucleic acids, and oligosaccharides, among other therapeutic macromolecular substances, are widely expected as innovative therapeutics for a variety of diseases. Drug discovery has traditionally focused on the synthesis of hydrophilic and highly absorbable small molecules (0.5 kDa) for oral drug therapeutics, but low molecular weight peptide and protein-like compounds (i.e., within the range of 0.5 kDa-5.0 kDa) are attractive alternatives due to their specificity, efficacy, and low toxicity when compared to synthetic small molecule drugs. Furthermore, low-molecular-weight peptides and protein-like compounds may have additional benefits, such as a lower cost of manufacture compared to high-molecular-weight pharmaceuticals (> 150 kDa) and the ability to create vast quantities of protein/antibody. Cyclic peptides, in particular, combine multiple features, including high affinity, target selectivity, and stability (enzymatic and chemical).

Because the majority of clinically authorised cyclic peptides are now sourced from natural sources, new cyclic peptides are anticipated to become a prominent drug development target in the future. However, there are a number of significant challenges in the development of orally given cyclic peptide therapies, the most significant of which is limited bioavailability due to low intestinal permeability. As a result, it's critical to understand the physiological mechanisms that control cyclic peptide intestinal penetration. After oral administration, cyclic peptides are mostly absorbed by passive diffusion across the intestinal epithelial membrane, which is similar to how most lipophilic small-molecule medicines are absorbed. However, diverse absorption pathways must be considered since different variables will likely have varied impacts on cyclic peptide permeability. For example, most cyclic peptides are anticipated to interact with numerous components of gastrointestinal fluids before reaching the epithelial cell surface, assuming adequate solubility in the intestinal lumen. Although various biological variables have been identified as regulating the intestinal permeability of cyclic peptides, the impact of the mucus barrier on cyclic peptide absorption is yet unknown. Mucus coats the surface of secretory epithelia like the intestinal and respiratory epithelia, acting as a dynamic barrier to pathogens and foreign particles under healthy circumstances. The mucins, which are polymeric, high-molecular-weight, extensively O-glycosylated proteins, are the key structural components of this complex hydrogel, which includes water,

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ions, and hundreds of proteins. Mucins produce viscoelastic gel-like networks that operate as a biological molecular sieve with hole diameters ranging from 20 to 400 nm, allowing foreign particles like as poisons, pathogens, and nanomaterials to be excluded. Mucins can also operate as a selective physical barrier by attaching to negatively charged O-glycans clustered in the highly glycosylated core domains and hydrophobic, non-O-glycosylated cysteine-rich regions due to their complex chemical makeup. Mucins' barrier qualities are important considerations in medication absorption in the intestine9. Mucus, on the other hand, is a dynamic barrier, with different compositions (especially mucin composition) and biological activities depending on the mucosal tissue. Although mucins have the potential to operate as key physiological regulators of medication absorption in the intestine (including cyclic peptides), the molecular mechanism for this control remains unknown.

As a result, characterising the effect of various mucins on cyclic peptide diffusion is critical in order to understand their possible impact on bioavailability and drug absorption. As a result, we studied the interaction of various cyclic peptides with three polymeric mucins that are important components of saliva (MUC5B), intestinal (MUC2), and stomach mucus (MUC2) (MUC5AC). We studied the interaction of isolated human polymeric mucins with cyclic peptides (daptomycin, polymyxin B, and cyclosporin A) known to be produced from natural products with various physicochemical features (e.g., lipophilicity and physiological charge) (MUC2, MUC5AC and MUC5B). We looked at the sedimentation behaviour of polymeric mucins to see if interaction with cyclic peptides caused structural changes in the mucin network.