

Lessons for Oral Bioavailability: How Conformationally Flexible Cyclic Peptides Enter and Cross Lipid Membranes

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Cyclic peptides can extend the druggable space of pharmaceutical targets, due to their size, conformational behavior, and high proportion of hydrogen bond donors and acceptors. However, for the same reasons, they often suffer from poor membrane permeation and thus low oral bioavailability. As permeability assays do not allow to monitor the pathway and behavior of cyclic peptides on their 'journey' through lipid membranes, little is known about the underlying permeation process, which poses a major obstacle for their rational design.

Here, we use molecular dynamics (MD) simulations as a computational microscope to uncover how large and conformationally flexible cyclic peptides enter and cross a lipid bilayer. Based on our simulations, we show how specific side-chain residues can act as 'molecular anchors', which establish the first contact between the peptides and the membrane, and consequently enable membrane insertion. Inside the membrane, the cyclic peptides are positioned directly between the polar headgroup and the apolar tail region, where they are subjected to a unique polar/apolar interface environment. In this environment, the cyclic peptides show a preference for one of two distinct orientations. We observe that only one of these orientations allows the formation of the permeable 'closed' conformation, and only in this 'closed' conformation the cyclic peptides can cross from the upper to the lower membrane leaflet, which again requires a unique anchoring and flipping mechanism. Our findings provide atomistic insights into the permeation process of flexible cyclic peptides and reveal unique design considerations for each step of the process.

