T-20 and T-1249 HIV fusion inhibitors' structure and conformational behavior in solution: a molecular dynamics study

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Fusion of the HIV envelope with the target cell membrane is a critical step of HIV entry into the target cell. Several peptides based on the C-region of HIV gp41 have been used in clinical trials as possible HIV fusion inhibitors. Among these are T-1249 and T-20 (also known as enfurvitide; see fig. 1). Despite recent works, a detailed molecular picture of the inhibitory mechanism of these molecules is still lacking. These peptides are usually depicted as α-helices by analogy with the structure of the sequence of the gp41 protein with which they are homologous. However, structures like these would not explain the ability that the two fusion inhibitors have to both become solvated by water and interact effectively with cell membranes.

This led us to study the structure and conformational behavior of all these peptides. To this effect, extensive molecular dynamics simulations (total time 400 ns) with explicit solvent (SPC water) were carried out to investigate the structure and conformational behavior of T-1249 and T-20, as well as shorter homologous peptides CTP and 3f5 (see fig. 1), which show no inhibitory action. The monitored parameters include mean square displacement relative to the initial conformation (α-helix structures in all cases), secondary structure, solvent accessible surface and radius of gyration. We found that the studied peptides have no stable structure in solution in the time scale studied. Additionally, the solvent accessible area varies significantly during the simulation. Our findings suggest that these peptides may assume not only one but several possible sets of structures in solution, some of which more adequate to interact with the solvent, whereas others might be better suited to interact with cell membranes.

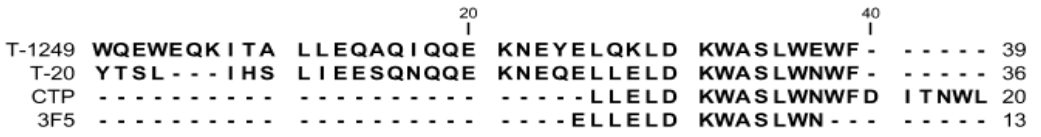

Fig. 1