INHIBITION OF F_1F_O-ATP SYNTHASE BY PHENOTHIAZINE STUDIES USING MOLECULAR DOCKING METHODS

Assis, J.M.L.; Rodrigues, T.; Nantes, I.L.; Shida, C.S.
Centro Interdisciplinar de Investigação Bioquímica, Universidade de Mogi das Cruzes, Mogi das Cruzes, Brazil

ATP is a molecule synthesized by F_1F_0-ATP synthase at mitochondrion complex V. Previous experimental studies of ATP synthesis in the presence of TFP (Trifluorperazine), a medicine from phenothiazine family and very popular antipsychotic in Brazil, showed a diminution in F_1F_0-ATP synthase activity. In the literature, *in vitro* studies suggest that ATP synthesis decreases due to competition of TFP with ADP by F_1F_0-ATP synthase active site. Using computational tools we have studied molecular mechanisms of F_1F_0-ATP synthase active site inhibition by TFP. The tridimensional structures of F_1F_0-ATP synthase used were those crystallized in the presence of ADP. Structures of mitochondrial bovine, human, and rat F_1F_0-ATP synthase, from Protein Data Bank, were used as model. Docking algorithms used were ArgusLab and Dock. Both algorithms permit docking studies with flexible ligands. We have observed that TFP is able to dock at the active site of human, bovine and rat F_1F_0-ATP synthases. TFP docking to different active sites of different F_1F_0-ATP synthases has presented, in most of the cases, the same conformational docking pattern. Distance measurements between different residue atoms of F_1F_0-ATP synthase and atoms of ligand TFP have confirmed, quantitatively, the repetition of the docking patterns. These results suggest that TFP inhibit the F_1F_0-ATP synthase by docking at its active site.