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Ligand Interactions and Ligand-Induced Conformational States of the Serotonin Transporter.

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The serotonin (5-HT) transporter (SERT) is the main molecular target for the selective serotonin reuptake inhibitors (SSRIs), currently the most prescribed antidepressant drugs. As the three dimensional (3D) structure of SERT is unknown, the prokaryotic homologous leucine transporter (LeuT) crystal structure of *Aquifex aeolicus* was used as a template to generate a homology model of SERT. Docking of substrates (tryptamine derivatives) and one inhibitor (S-citalopram) into the putative substrate binding site showed that the ligands may bind in two putative binding modes. In both binding modes, the protonated amine of the tryptamine derivatives was located near the D98 carboxyl side chain forming an ionic interaction, which is in accordance with experimental data. The two binding modes of the tryptamine derivatives differed in the orientation of the indole ring nitrogen and the orientation of the 5-position. In the most realistic binding mode of S-citalopram all sub-pockets of the putative substrate binding site were occupied. The amine moiety of the ligand was contained in the ionic sub-pocket, whereas the cyanophtalane and fluorophenyl moieties were located in the hydrophobic and aromatic sub-pockets, respectively. This binding mode is very similar to the binding mode suggested from mutational mapping of S-citalopram. Two 5-HT- and two S-citalopram-SERT complexes, as well as SERT alone, were embedded in a POPC lipid bilayer and >20 ns of molecular dynamics simulations were performed. The simulations indicated that substrate transport by SERT may involve the formation and breakage of ionic interactions and the winding and unwinding of α-helical structure.

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