Probing the Inhibitor Binding Site of Neurotransmitter Symporters Using FEP Calculations

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Dopaminergic pathways comprise a significant portion of the motor control and reward systems of the brain. The dopamine active transporter (DAT) concentrates dopamine in the presynaptic terminal by cotransporting ions down their concentration gradients. DAT is the target of several inhibitors, including the tricyclic antidepressants (TCAs) desipramine, clomipramine, and imipramine. Crystal structures of the homologous bacterial transporter, LeuT, have been solved with these inhibitors bound. The inhibitors were parameterized in the CHARMM force field by performing free energy perturbation (FEP) calculations of LeuT—TCA binding and comparing the results to experimental values. Using a mouse DAT homology model, further FEP calculations will be performed to simulate the mutation of residues important for TCA binding. These will be compared to experimental mutagenesis studies to better elucidate the characteristics of the mDAT inhibition site. A greater understanding of mammalian DAT inhibition may support research into DAT physiology and drug design.