The ins and outs of transport and inhibition of Organic Cation Transporter 1

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Organic Cation Transporter 1 (OCT1) plays a crucial role in hepatic uptake by mediating the transport of a range of metabolites and drugs. Genetic variations can alter the efficacy and safety of compounds transported by OCT1, in particular for metformin, a front-line drug used in the treatment of type II diabetes. Despite its importance in drug pharmacokinetics, the substrate selectivity and underlying structural mechanisms of OCT1 function remain poorly understood. Here we present cryo-EM structures of full-length human OCT1 in both ligand-free and drug-bound conditions, demonstrating the basis for its broad substrate recognition and transport. Comparison of structures of OCT1 in inward-open and outward-open conformations provides molecular insight into the alternating access mechanism of OCTs. In combination with molecular dynamics simulations and transport uptake studies, the structures of OCT1 complexed with different compounds illustrate the chemical basis for different mechanisms of transport and affinity. These results lay the foundation for understanding polyspecificity and the mechanism of transport in OCT1, allowing for better models and predictions of the interactions of other drugs and the effect of genetic polymorphisms on transport.