Structural insights into vesicular monoamine transport and neurological drug interactions

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Biogenic monoamines, crucial transmitters orchestrating neurological, endocrinal, and immunological functions, are stored in secretory vesicles by vesicular monoamine transporters (VMATs) for controlled quantal release. VMATs harness proton antiport to enrich monoamines ~10,000-fold and sequester neurotoxicants. VMATs are targeted by an arsenal of therapeutic drugs and imaging agents to treat and monitor neurodegenerative disorders and drug addiction. However, the structural mechanisms underlying VMAT function and drug interaction remain largely unknown. Here, we report a series of cryo-electron microscopy structures of human VMAT1 and VMAT2 with monoamines and drugs in multiple conformations (Ye et al, *Nature*, in press). VMAT1 structures are determined with four monoamines, the Parkinsonism-inducing MPP+, the psychostimulant amphetamine, and the antihypertensive drug reserpine. The structures reveal that a favored transition to lumenal-open state contributes to monoamine accumulation, while protonation facilitates the cytoplasmic-open transition and prevents monoamine binding to avoid unintended depletion. Monoamines and neurotoxicants share a binding pocket possessing polar sites for specificity and a wrist-and-fist shape for versatility. VMAT2 structures highlight a partially occluded, unbound state that blocks reverse transport to facilitate monoamine accumulation, and a fully occluded state for tetrabenazine binding. Amphetamine induces VMAT2 into a conformation that enables monoamine competition for psychostimulatory release. Structural comparisons between VMAT1 and VMAT2 reveal similarities in their mechanisms of monoamine accumulation and differences in substrate preferences and conformational flexibility. These structural and functional insights provide a deep understanding to the mechanisms of vesicular monoamine transport, and lay the foundation for developing novel therapeutics for neurodegenerative diseases and substance abuse.