VMAT2 Transport and Inhibition Mechanisms Revealed by Cryo-EM

Neurotransmitters are a class of signaling chemicals, including monoamines such as serotonin, dopamine, and histamine, which play a vital role in a variety of neurological activities, including mood, memory, growth and development, and drug addiction. The cytosolic neurotransmitters in presynaptic neurons must be transported into synaptic vesicles for storage and subsequent release. The package of monoamines into vesicles is mediated by the vesicular monoamine transporter protein VMAT2. Importantly, several drugs that target on VMAT2 have been used to treat hypertension and hyperactivity disorders.

Human VAMT2 is a small membrane protein with a molecular weight of only 56 kDa, making it extremely difficult for cryo-EM analysis. Prof. JIANG Daohua's group at the Institute of Physics (IOP) of the Chinese Academy of Sciences (CAS) successfully overcame the challenges by screening fusion proteins, and reconstructed the high-resolution structures of VMAT2 binding to three clinical drugs and the substrate serotonin. Combining with functional experiments and molecules dynamic simulations, they described the molecular mechanisms of substrate recognition and drug inhibition of VMAT2.

The cryo-EM structures were determined in cytoplasm facing, occluded and lumen facing states, representing three typical conformations in the transport cycle of VMAT2. The structures also revealed the inhibitory mechanisms of different drugs. For example, reserpine competes with serotonin for binding to the cytoplasm facing VMAT2, but tetrabenazine and ketanserin stabilize VMAT2 in occluded and lumen facing states, respectively. In addition, the structures provide important insights into understanding the distinct pharmacological properties of reserpine, tetrabenazine and ketanserin. Moreover, the serotonin-bound VMAT2 adopts a lumen-facing conformation, a state favoring substrate release.

This study advances the comprehension of VMAT2 functions and facilitates the mechanistic understanding of substrate recognition, drug inhibition, and drug development of VMAT2. Meanwhile, the strategy of VMAT2 fusion protein used in this study could be applied to other small membrane proteins, which will facilitate the structure analysis of membrane transporter proteins and other small proteins by cryo-EM.

This study entitled "Transport and inhibition mechanism of human VMAT2" was published in *Nature*.

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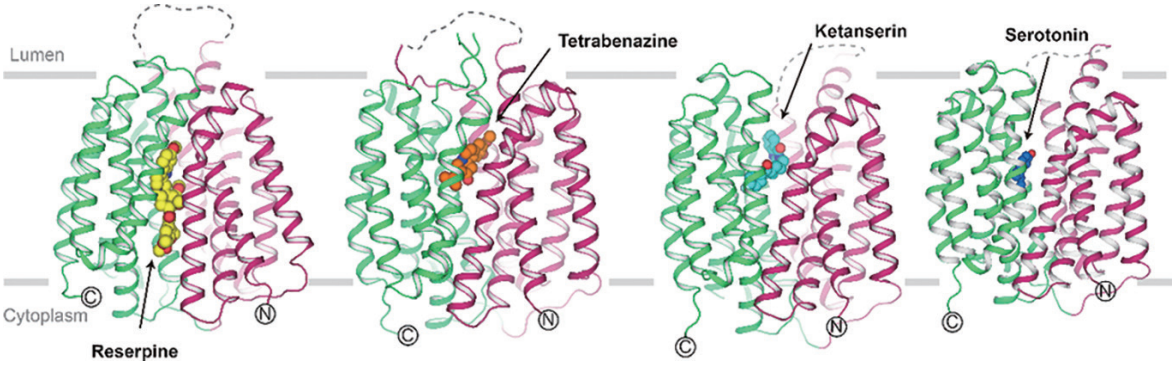

Cryo-EM structures of VMAT2 in complex with distinct ligands. (Image by IOP)

(IOP)