Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Colloquium

Structural and mechanistic insights into GABA recognition and transport inhibition in GABA transporters

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The plasma membrane neurotransmitter transporter, GAT1 is responsible for clearance of inhibitory neurotransmitter g-aminobutyric acid (GABA) from synaptic cleft. Targeting GABA reuptake by inhibiting GAT1, hence prolonging GABAergic signalling is one of the strategies to treat disorders arising due to imbalance in inhibitory neurotransmission like epilepsy and anxiety. To understand the mechanism of GABA recognition and transport, initially we used an engineered Drosophila melanogaster dopamine transporter to resemble GAT1 ($dDAT_{GAT}$) and determined high-resolution X-ray structures of the modified transporter in the substrate-free state and in complex with GAT1-inhibitors NO711 and SKF89976a. We further determined the cryo-EM structure of GAT1 from Rattus norvegicus at 3.1 Å resolution in a cytosol-facing conformation utilising a strategy of transferring the epitope for a fragment-antigen binding (Fab) interaction site, from Drosophila dopamine transporter (dDAT) to rGAT1, to assist structure determination through Fab binding to rGAT1 epitope construct. The structure captured a transport cycle intermediate step of rGAT1 with substrate GABA, tightly bound chloride, and a partly displaced sodium from site 1. GABA interacts in the binding pocket in a pose similar to GAT1 specific inhibitors in the $dDAT_{GAT}$ structure. This study highlights important details of the GABA recognition, transport activity and inhibition.

Monday, Apr 29th 2024

16:00 Hrs (Tea / Coffee 15:45 Hrs)

Auditorium, TIFR-H