The split personality of glutamate transporters: a chloride channel and a transporter

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Glutamate is the predominant excitatory neurotransmitter in the mammalian central nervous system and activates a wide range of receptors to mediate a complex array of functions. To maintain efficient synaptic signaling and avoid neurotoxicity, extracellular glutamate concentrations are tightly regulated by a family of glutamate transporters termed Excitatory Amino Acid Transporter (EAATs). Altered glutamate transmission, and specifically disrupted EAAT function, has been implicated in a range of disease states including; Alzheimer's disease, episodic ataxia, epilepsy and stroke. In addition to clearing glutamate from the extracellular space, EAATs can also function as chloride (Cl^-) channels, which contributes to ionic/osmotic balance and can affect cell excitability. The dual transporter/channel functions are mediated by distinct conformational states of the transporter and we have mapped the Cl^- permeation pathway to the interface of the transport and scaffold domain of the glutamate transporters. The EAATs use a unique mode of transport termed the 'twisting elevator' mechanism and we hypothesize that the Cl^- channel is activated during the elevator movement. Our aim is to develop a model for the dual functions of the glutamate transporters through structural and functional analysis of human (EAAT1) and prokaryotic (Glt_{Ph}) transporters. We have created a range of double cysteine mutants in cysteine-less EAAT1 and Glt_{Ph} to explore the movement of the transport domain during substrate translocation and to elucidate the conformational state/s that support an open Cl^- channel.