Tuning the ion selectivity of glutamate transporter associated uncoupled conductances

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The concentration of glutamate within a glutamatergic synapse is tightly regulated by excitatory amino acid transporters (EAATs). In addition to their primary role in clearing extracellular glutamate, the EAATs also possess a thermodynamically uncoupled Cl^- conductance. We have mapped the Cl^- permeation pathway to the interface of the transport and scaffold domain of the glutamate transporters and predict that an arginine residue at the most restricted part of this pathway might play a role in determining anion selectivity. In this study, we mutate this arginine to a histidine in the human glutamate transporter EAAT1 and investigate the role of the protonation state of this residue on anion selectivity and transporter function. Our results demonstrate that a positive charge at this position is crucial for determining anion *versus* cation selectivity of the uncoupled conductance of EAAT1. In addition, because the nature of this residue influences the turnover rate of EAAT1, we reveal an intrinsic link between the elevator movement of the transport domain and the Cl^- channel.