Colloquia in Cellular Signaling

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Insights into Permeation and Gating Mechanisms in EAAT Anion Channels by Computational Electrophysiology Simulations

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Abstract:

Glutamatergic synaptic transmission critically depends on excitatory amino acid transporters (EAATs) that remove the released neurotransmitter from the synaptic cleft and thereby ensure low extracellular glutamate concentrations in the central nervous system. EAATs are thermodynamically coupled glutamate/Na^+/H^+/K^+ transporters and anion selective channels. EAAT anion channels control neuronal excitability and synaptic communication, and their physiological importance is further corroborated by the recently identified association of altered EAAT anion conduction with neurological disorders. While X-ray crystallography has provided important structural insights into secondary active glutamate transport, the molecular mechanisms underlying anion permeation could only recently be resolved by a combination of electrophysiology, spectroscopy and molecular simulations (1, 2). Computational Electrophysiology (CompEL) is a recently developed protocol for molecular dynamics simulation of membrane proteins under sustained electrochemical potential gradients (3). CompEL can be used to simulate and quantify ion permeation, calculate reversal potentials, and determine gating charges and capacitance changes of ion channels and transporters. In this talk, I will discuss recent insights into permeation and gating mechanisms in EAAT anion channels by Computational Electrophysiology simulations.

*1. Machtens, J. P., Kortzak, D., Lansche, C., Leinenweber, A., Kilian, P., Begemann, B., Zachariae, U., Ewers, D., de Groot, B. L., Briones, R., and Fahlke, C. (2015) Mechanisms of anion conduction by coupled glutamate transporters. Cell **160**, 542-553.*
*2. Fahlke, C., Kortzak, D., and Machtens, J. P. (2016) Molecular physiology of EAAT anion channels. Pflugers Arch **468**, 491-502.*
*3. Kutzner, C., Kopfer, D. A., Machtens, J. P., de Groot, B. L., Song, C., and Zachariae, U. (2016) Insights into the function of ion channels by computational electrophysiology simulations. Biochim Biophys Acta **1858**, 1741-1752.*