MS018.O04

Driving a wedge into the TREK channel heart

Daniel Minor[1]
[1]*UCSF Cardiovascular Research Institute, San Francisco, United States*
E-mail: daniel.minor@ucsf.edu

Polymodal K2P thermo- and mechanosensitive TREK potassium channels, generate 'leak' currents that regulate neuronal excitability, respond to lipids, temperature, and mechanical stretch, and influence pain, temperature perception, and anesthetic responses. These dimeric voltage-gated ion channel superfamily members have a unique topology comprising two pore forming regions per subunit. Contrasting other potassium channel classes, K2Ps use a selectivity filter 'C type' gate as the principal gating site [1, 2]. Similar to many ion channel classes, K2Ps suffer from a poor pharmacologic profile that limits mechanistic and biological studies. We identified a new small molecule TREK activator class that directly stimulates the C type gate by acting as molecular wedges that restrict interdomain interface movement behind the selectivity filter. X-ray crystal structures of K2P2.1(TREK-1) alone and with two selective activators, define a cryptic binding pocket unlike other ion channel small molecule binding sites. Together, our data unveil a previously unknown, druggable K2P site that stabilizes the C-type gate 'leak mode' and provide direct evidence for K2P selectivity filter gating [3].

[1] S. N. Bagriantsev, et al. (2011). EMBO J. 30 3594-606
[2] M. Schewe et al. (2016). Cell. 164 937-49
[3] M. Lolicato et al. (2017) Nature 10.1038/nature22988

Keywords: K2P potassium channel, small molecule activator, pharmacology