The molecular basis for an allosteric inhibition of k+-flux gating in k2p channels

Rinné S.

Kiper A.K.

Vowinkel K.S.

Ramírez D.

Schewe M.

Bedoya M.

Aser D.

Gensler I.

Netter M.F.

Stansfeld P.J.

Baukrowitz T.

Gonzalez W.

Decher N.

Two-pore-domain potassium (K2P) channels are key regulators of many physiological and pathophysiological processes and thus emerged as promising drug targets. As for other potassium channels, there is a lack of selective blockers, since drugs preferentially bind to a conserved binding site located in the central cavity. Thus, there is a high medical need to identify novel drug-binding sites outside the conserved lipophilic central cavity and to identify new allosteric mechanisms of channel inhibition. Here, we identified a novel binding site and allosteric inhibition mechanism, disrupting the recently proposed K+-flux gating mechanism of K2P channels, which results in an unusual voltage-dependent block of leak channels belonging to the TASK subfamily. The new binding site and allosteric mechanism of inhibition provide structural and mechanistic insights into the gating of TASK channels and the basis for the drug design of a new class of potent blockers targeting specific types of K2P channels. © Rinné et al