

Study Furthers Development of Drugs Targeting Potassium-Ion Channels

Scientific Achievement

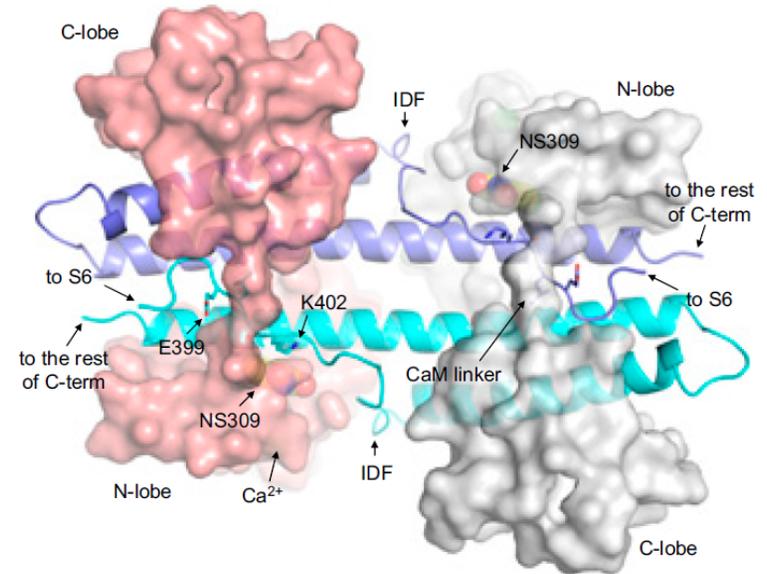
Determined that a potential drug targeting potassium-ion (K^+) channels, known as NS309, works by stabilizing the structure of an “intrinsically disordered” channel fragment (IDF)

Significance and Impact

Study aids the development of NS309 and other compounds that target K^+ channels, which could treat cardiovascular and nervous system disorders

Research Details

- K^+ channel is activated by calcium ions (Ca^{2+}), which are sensed by a protein called calmodulin (CaM) bound to the calmodulin binding domain (CaMBD)
- Channel contains an IDF that is a target for pharmaceuticals but is difficult to investigate by standard methods because of its changing conformations
- Using x-ray crystallography, researchers studied a crystal of CaM and CaMBD in complex, and then a second crystal of CaM, CaMBD, and NS309
- The IDF appeared when NS309 was present, taking on a distinctive conformation that helped couple the Ca^{2+} to the calmodulin and, as a result, a unique role in the mechanical opening of the channel



Structure of the entire CaM/CaMBD complex in the presence of NS309, showing the stabilized IDF

Work was performed at Brookhaven National Laboratory, Lawrence Berkeley National Laboratory, and Thomas Jefferson University

M Zhang, JM Pascal, J-F Zhang, *PNAS* **110** (10), 4828-4833 (2013)