MedChem & CADD-2013
2nd International Conference on
Medicinal Chemistry & Computer Aided Drug Designing
October 15-17, 2013 Las Vegas, USA

Harnessing human N-type Ca^{2+} channel receptor by identifying the atomic hotspot regions for its blocker design

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Abstract

Voltage-gated N-type Ca^{2+} channels (NCCs) play dominant roles in neuropathic pain and cerebral ischemia. Ion channel therapeutics for many pathophysiological conditions exists, which include: affective disorders, allergic disorders, autoimmune diseases, epilepsy, hypertension, insomnia, pain, anesthesia, anxiety, and stroke. Experimentally, it was well established that NCC inhibitory activity is essential for the treatment of chronic neuropathic pain and stroke. A major obstacle with these membrane proteins is that the atomic resolution experimental structures are not available to understand the mode of small molecule binding at its active sites.

Based on these observations, we have developed for the first time the structure of the closed state of the NCC receptor at the pore forming domains which mainly involve three transmembrane helices (TMhs) S5, P and S6. Hot-spot binding site residues of this receptor model were identified by molecular docking technique using amlodipine, cilnidipine and nifedipine compounds known to be potent Ca^{2+} channel antagonists. Further, the Ca^{2+} ion permeability and the hydrophobic gating mechanism provided better structural and functional insights on the NCC receptor. These results are in consonance with other Ca^{2+} channel receptors and would provide guidance for further biochemical investigations.

Biography

Dr. C Gopi Mohan is currently an Associate Professor at Amrita Centre for Nanoscience and Molecular Medicine specializing in the area of Structural bioinformatics, Chemoinformatics, Nanoinformatics and its biomedical applications. Currently, his team at centre focuses on: Structure-based Drug design, Pharmacophore modeling, QSAR modeling and Nanomaterial modeling using different *in silico* techniques. He worked as a faculty member of National Institute of Pharmaceutical Education & Research (NIPER), Mohali, Punjab and also as a post doctoral fellow in Indian Institute of Science, Bangalore; University of Bath, UK and CNRS research fellow at University Henri Poincare, France. He had been recipient of Indo-Finland grant for computational biology related to drug development and visited University of Helsinki and University of Turku to complete successfully this collaborative bilateral program. His protein models and other related computational work was appreciated by US based pharmaceutical company leading to future collaboration. He was also cited as international well known expert in the field of Structural Bioinformatics and Chemoinformatics by Synergix Ltd. United Kingdom, which was founded by Dr. N.C. Cohen, a pioneer of rational drug design.