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

Inward rectifier potassium channels as emerging drug targets

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Abstract

An emerging body of genetic and physiological evidence suggests that certain members of the inward rectifier potassium (Kir) channel family represent novel drug targets for several common diseases. With few exceptions, however, the molecular pharmacology of the family has remained essentially undeveloped since the first member was cloned more than two decades ago. The Renal Outer Medullary K^+ channel (ROMK), or Kir1.1, plays pivotal roles in the regulation of fluid-volume and electrolyte homeostasis by the kidney. Heritable loss-of-function (LOF) mutations in ROMK in patients with Type 2 Bartter syndrome lead to renal salt wasting and lower blood pressure. Similarly, LOF mutations in the gene encoding Kir4.1 lead to SeSAME/EAST syndrome, a complex disorder presenting with renal salt-wasting, low blood pressure, and neurological deficits. High-throughput screening of the NIH Molecular Libraries Small-Molecule Repository, medicinal chemistry, electrophysiology, and molecular modeling are being used to develop tool compounds for interrogating the therapeutic potential of Kir1.1 and Kir4.1 as novel diuretic targets. Progress toward developing inhibitors of mosquito Kir channels for use as insecticides to limit the transmission of malaria and other debilitating vector-borne diseases will also be discussed.

Biography

Dr. Denton earned a PhD in integrative physiology from Dartmouth College in 2002 and went on to do postdoctoral training with Kevin Strange at Vanderbilt University. He joined the faculty in the Departments of Anesthesiology and Pharmacology at Vanderbilt in 2005, where his lab has focused on developing the molecular pharmacology for the inward rectifier potassium channel family. His lab has been funded by grants from the American Heart Association, National Kidney Foundation, the NIH and Foundation for the NIH.