PHYSIOLOGY & MEMBRANE BIOLOGY

SCHOOL OF MEDICINE

UNIVERSITY OF CALIFORNIA AT DAVIS

DISTINGUISHED SPEAKER SERIES

William Catterall, Ph.D.
Professor & Chair
Department of Pharmacology
University of Washington, School of Medicine

"Voltage-gated Sodium Channels at Atomic Resolution: Structure, Function, and Disease"

Voltage-gated sodium channels initiate electrical signaling in excitable cells and are the molecular targets for drugs and disease mutations. The crystal structure of a bacterial voltage-gated sodium channel (NavAb) with a closed-pore and four activated voltage-sensors at 2.7 Å resolution has given new insight into gating, ion selectivity, and drug block. In the voltage sensor, arginine gating-charges make multiple hydrophilic interactions including unanticipated hydrogen bonds to the protein backbone. Comparisons to previous open-pore potassium channel structures suggest that the voltage-sensor domains and the S4-S5 linkers dilate the central pore by pivoting together around a hinge at the base of the pore module. The NavAb selectivity filter is short, ~4.6 Å wide, and water-filled, with four acidic side-chains surrounding the narrowest part of the ion-conduction pathway. This unique structure presents a high field-strength anionic coordination site, which confers sodium-selectivity through partial dehydration via direct interaction with glutamate side-chains. Fenestrations in the sides of the pore are unexpectedly penetrated by fatty-acyl chains that extend into the central cavity, and these portals are large enough for entry of small, hydrophobic pore-blocking drugs directly at the location of the local anesthetic receptor site. Sodium channels are the targets of a broad range of disease mutations that affect all aspects of their function. Remarkably, gain-of-function mutations that cause state-dependent ionic leak through the voltage sensor are responsible for Hypokalemic Periodic Paralysis. Our new structural information reveals the molecular basis for the ionic leak caused by these disease mutations at the atomic level.

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10:00 am

Genome and Biomedical Sciences Facility
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