



Biomedical Engineering Seminar Series



Johns Hopkins School of Medicine and the Whiting School of Engineering

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NIH/NINDS



Monday, November 23, 2009 at 1:30

Talbot Room, Traylor 709

Host: Dr. David Yue

Light lunch will be provided in Traylor 709

Video-Teleconferenced to Homewood Campus,
Rome Room, Clark 110

Structural basis of voltage sensor function and pharmacology in ion channels

Voltage-activated potassium (Kv), sodium (Nav) and calcium (Cav) channels are crucial for generating and propagating nerve impulses, and as such are widely targeted by toxins and drugs. Although identifiable S1–S4 voltage-sensing domains are found in voltage-activated ion channels and in other membrane proteins that lack associated pore domains, the extent to which their voltage-sensing mechanisms are conserved is unknown. In addition, the four voltage sensors in Nav and Cav channels have distinct amino acid sequences, in contrast to Kv channels where they are identical, raising fundamental questions about the relative contributions of individual voltage sensors to the function and pharmacology of Nav and Cav channels. I will describe experiments showing that the voltage-sensor paddle, a motif composed of S3b and S4 helices, is a modular and portable structural motif that moves in the relatively unconstrained environment of the lipid membrane in a wide range of channels and membrane proteins with voltage-sensing domains. I will talk about studies showing that paddle motifs are widely targeted by toxins that partition into membranes to interact with paddle motifs at the protein–lipid interface and how we use four-fold symmetric Kv channels as reporters to examine the contributions of individual paddle motifs within Nav channel voltage sensors to the function and pharmacology of those channels. I will also discuss how toxins can detect the presence of specific lipid species bound to the paddle motif and how voltage sensors influence the structure of the surrounding lipid membrane.

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