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Research Interests

Voltage-gated Na⁺ channels are responsible for action potential initiation and conduction in excitable cells. In myelinated neurons, Na⁺ channels are clustered at high density in specialized, subcellular domains such as nodes of Ranvier and axon initial segments. What is the mechanism responsible for Na⁺ channel localization and clustering? What proteins make up the Na⁺ channel signaling complex? We have shown that Na⁺ channels are unique among voltage- and ligand-gated ion channels in that they contain auxiliary subunits that not only modulate channel kinetics, but also function as cell adhesion molecules (CAMs) that direct channel insertion into the plasma membrane and channel interaction with other signaling proteins. We propose that, as CAMs, Na⁺ channel beta subunits act as critical communication links between extra- and intracellular signaling molecules in excitable cells.

Voltage-gated Na⁺ channels isolated from mammalian neurons are heterotrimeric protein complexes composed of alpha and beta subunits. The mammalian pore-forming alpha subunits encode a gene family of at least ten members. The beta subunit gene family consists of four members: beta 1, beta 2, beta 3, and beta 4. Beta1A, a splice variant of beta 1 expressed in embryonic brain, has also been described. Alpha subunit cDNAs express functional Na⁺ channels in heterologous expression systems such as *Xenopus* oocytes or mammalian fibroblasts. However, for "brain" (TTX-sensitive) alpha subunits, the currents characteristic of these channels expressed in isolation are quite different from native currents. Co-expression of the beta subunits with these channels results in hyperpolarizing shifts in the voltage-dependence of activation and inactivation, changes in channel modal gating behavior resulting in increases in the rates of inactivation and recovery from



inactivation, and increases in channel density at the plasma membrane as assessed by 3H-saxitoxin (STX) binding. Na⁺ channel beta subunits and the beta subunits of voltage-gated Ca²⁺ and K⁺ channels are functionally homologous in terms of channel modulation. However, Ca²⁺ and K⁺ channel beta subunits are not structurally homologous to Na⁺ channel beta subunits and only the Na⁺ channel beta subunits have been shown to function as CAMs in addition to their roles in channel modulation. Thus, the Na⁺ channel beta subunits present a unique opportunity to study cell adhesion in terms of electrical signal transduction.

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