

Distinguished Lecture Series in Physiology

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“The Cardiac Sodium Channel: Lessons Learned from Bedside to Bench”

Modification in Na⁺ current (I_{Na}) is known to contribute to both cardiac arrhythmias from acquired heart diseases and inherited cardiac arrhythmias. Since the original cloning of the genes encoding for voltage-gated sodium channels and the recording of its function by patch-clamping, the α -subunit of the sodium channel was thought to be a monomer. However, our studies of mutations found in *SCN5A* linked to different arrhythmic syndromes led us to question the traditional idea of the sodium channel forming a monomer. In fact, we and others have shown that several Brugada Syndrome (BrS) mutations display dominant-negative effects (DN-effect), which could only be attributed to interaction between α -subunits within multimeric complexes. Similarly, we have shown that the defects of several BrS or LQT3 *SCN5A* mutations could be rescued by different *SCN5A* polymorphisms expressed on a separate construct, again supporting the idea of an α - α subunit interaction. We demonstrated using different experimental approaches that sodium channels form functional dimers. We also identified the region modulating the dimerization and found that this physical dimerization results in coupled gating of the sodium channels and involves 14-3-3. We further demonstrated that the biophysical coupling is dynamically modulated. Understanding of the mechanisms involved in channel dimerization and functional biophysical coupling could open the door to new approaches and targets to treat and/or prevent sodium channelopathies and dysregulation of I_{Na} in heart failure.

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10



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