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Na channel dysfunction in inherited arrhythmias: The effect of common polymorphism, splice variant and intracellular acidosis

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The gene *SCN5A* on chromosome 3 encodes the α-subunit of the voltage-gated cardiac sodium channel (hNav1.5) that is responsible for large peak inward sodium current (I_{Na}) and late I_{Na}. Peak I_{Na} underlies excitability and conduction in working myocardium (atrial and ventricular cells) and special conduction tissues (Purkinje cells etc.). Late I_{Na} influences repolarization and refractoriness. The importance of I_{Na} for normal cardiac electrical activity is emphasized by the occurrence of potentially lethal arrhythmias in the setting of inherited and acquired Na channel diseases. *SCN5A* in humans has two splice variants, one lacking a glutamine at position 1077 (Q1077del) and one containing Q1077. Common sequence variants ("polymorphisms") have also been implicated as risk factors in multiple diseases. Mutations in the cardiac Na channel gene *SCN5A* cause loss-of-function or gain-of-function and underlie arrhythmia syndromes, such as Brugada syndrome, cardiac conduction disorder, congenital sick sinus syndrome, idiopathic ventricular fibrillation, sudden infant death syndrome, the type 3 long QT syndrome etc. Here, 3 unrelated inherited arrhythmia cases will be presented to show that the loss-of-function or gain-of-function biophysical phenotypes for sodium channel mutations depend on the splice variant background in which it is expressed and the intracellular acidosis, and is also modulated by common polymorphism.

Biography

Bi-Hua Tan was initially trained as a cardiologist in China after graduated from medical school. Then she joined the arrhythmia and clinical electrophysiological study group at Cardiovascular Division, Hyogo College of Medicine in Japan and obtained her PhD degree there. After that she completed her postdoctoral training at the Cellular and Molecular Arrhythmia Research Program, Department of Medicine, University of Wisconsin-Madison. She was the first to characterize the molecular phenotype of eight common polymorphisms and some genetic basis of disease causing mutations in cardiac Na channel. She also first characterized a marked gain of functional K_{ATP}Kir6.1 channel mutation in *KCNJ8* as a novel pathogenic mechanism for the phenotypic expression of both Brugada syndrome and early repolarization syndrome. She was awarded American Heart Association (AHA) Postdoctoral Fellowship and the American Heart Association National Center Scientist Development Grant

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