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A novel mechanism of SCN5A mutations causing mixed arrhythmias associated with dilated cardiomyopathy

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Cardiac Na+ channels encoded by the SCN5A gene are essential for initiating heart beats and maintaining a regular heart rhythm. Mutations in these channels have recently been associated with atrial fibrillation, ventricular arrhythmias, conduction disorders, and dilated cardiomyopathy (DCM). We investigated a young male patient with a mixed phenotype composed of documented conduction disorder, atrial flutter, and ventricular tachycardia associated with DCM. Further family screening revealed DCM in the patient's mother and sister and in three of the mother's sisters. Because of the complex clinical phenotypes, we screened SCN5A and identified a novel mutation, R219H, which is located on a highly conserved region on the fourth helix of the voltage sensor domain of Nav1.5. Three family members with DCM carried the R219H mutation. The wild-type (WT) and mutant Na+ channels were expressed in a heterologous expression system, and intracellular pH (pHi) was measured using a pH-sensitive electrode. The biophysical characterization of the mutant channel revealed an unexpected selective proton leak with no effect on its biophysical properties. The H+ leak through the mutated Nav1.5 channel was not related to the Na+ permeation pathway but occurred through an alternative pore, most probably a proton wire on the voltage sensor domain. We propose that acidification of cardiac myocytes and/or downstream events may cause the DCM phenotype and other electrical problems in affected family members. The identification of this clinically significant H+ leak may lead to the development of more targeted treatments.

Biography

Mohamed Chahine has completed his Ph.D. at the University of Poitiers in France. He is the director of the Cellular and Molecular Cardiology Laboratory at Laval University. He has published more than 100 papers in reputed journals. He has published several major papers on the underlying causes of the long QT syndrome, Brugada syndrome, and Paramyotonia Congenital in patients around the world, including some in Canada. Therefore his research is at the leading edge of studies on sodium channelopathies. He has been serving as an editorial board member of repute.

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