GATING-DEPENDENT MECHANISMS FOR FLECAINIDE INTOLERANCE IN SCN5A-LINKED ARRHYTHMIA SYNDROMES

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Mutations in the cardiac Na channel gene (SCN5A) give rise to inherited arrhythmia syndromes (Brugada and Long QT) which provoke life-threatening arrhythmias. It was observed (Priori, *Circulation*, 2000) that patients who carry LQT mutations may nevertheless experience, proarrhythmic effects in response to potent Na channel blockers (flecainide). Here we examine the flecainide sensitivity of a mutant Na channel, 1795insD, that exhibits features of both the Brugada and Long QT syndromes (Veldkamp, *Circ Res*, 2000). Using whole-cell sodium current (I_{Na}) recordings in tsA-201 cells, two distinct forms of drug sensitivity were identified and linked to specific 1795insD gating defects. (1) The mutation markedly enhanced inactivation from closed states immediately upon depolarization, and thereby potentiated flecainide-induced "tonic" block of peak I_{Na} (31±4% for 1795insD vs. 11±2% for WT, $p<0.001$). (2) 1795insD delayed recovery from inactivation due to augmentation of slow inactivation upon sustained depolarization, and recovery from flecainide block was further delayed (at -120mV, WT: 74±11ms vs. 1795insD: 324±47ms, $p<0.01$). These results provide a mechanistic framework for predicting increased tonic or use-dependent flecainide sensitivity based on specific Na channel functional defects associated with SCN5A mutations.