SYNERGISTIC EFFECT OF THE NOVEL MUTATIONS IN SCN5A AND SNTA1 ON LATE INA CONTRIBUTING TO LQT SYNDROME

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Objectives SCN5A and SNTA1 are reported susceptible genes for long QT syndrome (LQTS). This study was designed to elucidate a plausible pathogenic arrhythmia mechanism for the combined novel mutations R800L-SCN5A and A261V-SNTA1 on cardiac sodium channels.

Methods A Caucasian family with syncope and marginally prolonged QT interval was screened for LQTS-susceptibility genes and found to harbour the R800L mutation in SCN5A and A261V-SNTA1. The mutations were engineered into the most common splice variant of human SCN5A and SNTA1 cDNA respectively and sodium current (I_{Na}) was characterised in HEK293 cells co-transfected with neuronal nitric oxide synthase (nNOS) and the cardiac isoform of the plasma membrane Ca-ATPase (PMCA4b).

Results The peak I_{Na} densities did not differ between WT and mutant channels containing R800L-SCN5A, A261V-SNTA1 or R800L-SCN5A plus A261V-SNTA1. However, late I_{Na} for either mutant channel was moderately increased 2–3 fold compared to WT. The combined mutations of R800L-SCN5A plus A261V-SNTA1 significantly enhanced the I_{Na} late/peak ration by 5.6-fold compared with WT. The time constants of current decay of combined mutant channel were markedly increased. The 'gain-of-function' effect could be blocked by the NG-monomethyl-L-arginine (L-NMMA), a nNOS inhibitor.

Conclusions We conclude that novel mutations in SCN5A and SNTA1 synergistically exert a nNOS dependent 'gain-of-function' on SCN5A channels, which may consequently prolong the action potential duration (APD) and lead to LQTS phenotype.

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