Analyses of a novel SCN5A mutation (C1850S) : conduction vs : repolarization disorder hypotheses in the Brugada syndrome

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AIMS: Brugada syndrome (BrS) is characterized by arrhythmias leading to sudden cardiac death. BrS is caused, in part, by mutations in the SCN5A gene, which encodes the sodium channel alpha-subunit Na(v)1.5. Here, we aimed to characterize the biophysical properties and consequences of a novel BrS SCN5A mutation. METHODS AND RESULTS: SCN5A was screened for mutations in a male patient with type-1 BrS pattern ECG. Wild-type (WT) and mutant Na(v)1.5 channels were expressed in HEK293 cells. Sodium currents (I(Na)) were analysed using the whole-cell patch-clamp technique at 37 degrees C. The electrophysiological effects of the mutation were simulated using the Luo-Rudy model, into which the transient outward current (I(to)) was incorporated. A new mutation (C1850S) was identified in the Na(v)1.5 C-terminal domain. In HEK293 cells, mutant I(Na) density was decreased by 62% at -20 mV. Inactivation of mutant I(Na) was accelerated in a voltage-dependent manner and the steady-state inactivation curve was shifted by 11.6 mV towards negative potentials. No change was observed regarding activation characteristics. Altogether, these biophysical alterations decreased the availability of I(Na). In the simulations, the I(to) density necessary to precipitate repolarization differed minimally between the two genotypes. In contrast, the mutation greatly affected conduction across a structural heterogeneity and precipitated conduction block. CONCLUSION: Our data confirm that mutations of the C-terminal domain of Na(v)1.5 alter the inactivation of the channel and support the notion that conduction alterations may play a significant role in the pathogenesis of BrS.
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