Biophysical consequences of missense mutations associated with Brugada syndrome

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Background/Introduction: Brugada syndrome (BrS) is a rare inherited arrhythmogenic disease, characterized by high risk of sudden death. More than 200 missense mutations in cardiac voltage-gated sodium channel alpha-subunit gene (SCN5A) are described in association with this condition. However, biophysical mechanisms underlying the development of the arrhythmia are identified only for half of the mutations. Furthermore, relations between biophysical features of the mutant channels and clinical phenotype are not completely understood.

Here we identified two novel SCN5A mutations in patients with Brugada syndrome. Mutation Y739D in extracellular linker DII_S1-S2 leads to the classical clinical picture of BrS. Mutation A1294G in extracellular linker DIII_S3-S4 is responsible for complex clinical picture including Brugada-like ECG, fibrosis, cardiac dilatation and decreased left ventricular contractility. We explored biophysical properties of the two mutations and estimated their impact to loss-of-function phenotype and pathogenesis of the disease.

Methods: Mutations A1294G and Y739D were introduced in the SCN5A cDNA using site-directed mutagenesis. Sodium currents were recorded at the room temperature in CHO transfected cells. Electrophysiological measurements are presented as mean ±SEM.

Results: Mutation A1294G markedly decreased (62%) the peak current density (-381.8±18.2 pA/pF and 146.1±22.7 pA/pF for WT and A1294G, respectively) and increased two-fold slow time constant of recovery from inactivation. In contrast, mutation Y739D demonstrated a less marked reduction (38%) of INa (-285.6±27.7 pA/pF and -176.9±29.8 pA/pF for WT and Y739D, respectively) and 1.5-fold growth of slow time constant of recovery from inactivation. Patch-clamp measurements did not reveal significant alterations in the kinetic of steady-state activation, steady-state inactivation and the onset of slow inactivation of these mutant channels.

Conclusions: Deceleration of recovery from inactivation and decrease of INa contribute to the loss-of-function phenotype of mutations A1294G and Y739D. A possible relationship between electrophysiological properties and severity of clinical phenotype in patients with SCN5A-related Brugada syndrome is proposed.