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Recovery of Scn5a-deficient mice cardiac conduction using AAVs

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Introduction: Loss-of-function mutations in the cardiac Na⁺ channel a-subunit gene, SCN5A, cause Brugada syndrome (BrS), a hereditary disease characterized by ventricular fibrillation and sudden cardiac death. While complete deletion of the Na⁺ channel is lethal, heterozygous Scn5a+/⁻ mice have a Na⁺ current (INa) decreased by 50% and present slower atrioventricular and ventricular conduction, as well as ventricular arrhythmias, partly recapitulating the BrS patient symptoms. An alternative strategy to anti-arrhythmic drugs or implantation of a cardioverter-defibrillator, consisting in the cardiac-specific expression of a transgene rescuing the deficient Na⁺ current, would be promising to treat these arrhythmias. This project aims to overexpress the full human SCN5A gene using AAVs to rescue INa in Scn5a+/⁻ mice.

Methods: Because of the large size of the SCN5A gene, we used a dual AAV vector strategy to package the cardiac specific troponin-T promoter and the 5' half of SCN5A in one AAV, and the 3' half of SCN5A fused to the gfp reporter gene in a second AAV. Mice were injected with both serotype-9 AAV populations (Nav1.5-injected mice). Non-injected Scn5a+/⁻ mice were considered as controls. Eight weeks after injection, ECG and echocardiographic parameters were recorded. Mice were then sacrificed and their right ventricles were dissected to record action potentials (AP) using the intracellular microelectrode technique. The Na⁺ current was recorded by the patch-clamp technique after isolation of adult cardiomyocytes from Nav1.5-injected and control mice.

Results: Data showed a recovery of the atrioventricular and ventricular conduction in Nav1.5-injected Scn5a+/⁻ mice compared to control Scn5a+/⁻ mice (PR interval = 31.2 ± 1.4 ms in Nav1.5-injected Scn5a+/⁻ mice vs 42.1 ± 1.3 ms in control Scn5a+/⁻ mice vs 36.2 ± 0.9 ms in wild type (WT) mice; QRS interval = 12.5 ± 0.4 ms in Nav1.5-injected Scn5a+/⁻ mice vs 14.9 ± 0.4 ms in control Scn5a+/⁻ mice vs 13.2 ± 0.4 ms in WT mice). This was consistent with the large increase of INa detected in cardiomyocytes isolated from Nav1.5-injected Scn5a+/⁻ mice compared to control Scn5a+/⁻ mice (INa density at -30 mV = -151.8 ± 12.4 pA/pF in Nav1.5-injected Scn5a+/⁻ mice vs -36.9 ± 11.8 pA/pF in control Scn5a+/⁻ mice vs -77 ± 11.8 pA/pF in WT mice). We also observed an increase of the AP duration in Nav1.5-injected Scn5a+/⁻ mice compared to control Scn5a+/⁻ mice (APD90 at 1Hz = 67.3 ± 2.9 ms in Nav1.5-injected Scn5a+/⁻ mice vs 60.3 ± 3.3 ms in control Scn5a+/⁻ mice).

Conclusion: Overexpressing the full cardiac Na⁺ channel gene is highly efficient to rescue cardiac conduction of Scn5a+/⁻ mice. Further studies are needed to assess the effects of the overexpression of SCN5A on the occurrence of arrhythmias in Scn5a+/⁻ mice.