Abstract: P607

Mechanism of sinus node dysfunction in carriers of the E161K mutation in the SCN5A gene

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Background: Some but not all carriers of the E161K mutation in the SCN5A gene, which encodes the Nav1.5 pore-forming a-subunit of the ion channel underlying the cardiac fast sodium current (INa), show sinus bradycardia and occasional exit block. Voltage clamp experiments on wild-type and mutant INa channels in mammalian expression systems have revealed a mutation-induced 2.5 to 4-fold reduction in INa peak current density as well as a +19-mV shift and reduced steepness of the steady-state activation curve. The highly common H558R polymorphism in Nav1.5 limits the shift in steady-state activation to +13 mV, but also introduces a -10-mV shift in steady-state inactivation.

Purpose: We assessed the cellular mechanism by which the E161K mutation causes sinus node dysfunction in heterozygous mutation carriers as well as the potential role of the H558R polymorphism.

Methods: We incorporated the mutation-induced changes in INa into the Fabbri-Severi model of a single human sinoatrial node cell and the Maleckar et al human atrial cell model, and carried out computer simulations under conditions of normal autonomic tone and vagal tone.

Results: In H558 background, the E161K mutation increased the intrinsic cycle length of the sinoatrial node cell by 54 ms. Under vagal tone, through the simulated presence of 10–25 nM acetylcholine, this increase was raised to 104–347 ms, reducing the beating rate at 25 nM acetylcholine from 41 to 33 beats/min. The increase in cycle length was the result of a significant slowing of diastolic depolarization. The mutation-induced reduction in INa window current had reduced the contribution of the mutant component of INa to the net membrane current during diastolic depolarization to effectively zero. Highly similar results were obtained in R558 background. Atrial excitability was reduced, in either background, as reflected by an increase in threshold stimulus current and a concomitant decrease in capacitive current of the atrial cell.

Conclusions: We conclude that the experimentally identified mutation-induced changes in INa can explain the clinically observed sinus node dysfunction. Furthermore, we conclude that the common H558R polymorphism does not significantly alter the effects of the E161K mutation and can thus not explain the reduced penetrance of the E161K mutation.