Mechanism of Sinus Node Dysfunction in Carriers of the E161K Mutation in the *SCN5A* Gene

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Background: Carriers of the E161K mutation in the *SCN5A* gene, which encodes the $Na_v1.5$ pore-forming subunit of the cardiac fast sodium channel (I_{Na} channel), show sinus bradycardia, with a minimum heart rate of 39 ± 1 beats/min in mutation carriers (mean ± SEM, n = 10) vs. 51 ± 0.6 beats/min in non-carriers (n = 28), as well as occasional exit block. Voltage clamp experiments on wild-type and mutant I_{Na} channels in expression systems have revealed a mutation-induced 4-fold reduction in I_{Na} peak current density as well as a +19-mV shift in steady-state activation. The highly common H558R polymorphism in $Na_v1.5$ limits the shift in steady-state activation to +13 mV, but also introduces a −10-mV shift in the steady-state inactivation curve.

Aim: We assessed the mechanism by which the E161K mutation causes sinus bradycardia and reduces atrial excitability in heterozygous mutation carriers as well as the potential role of the H558R polymorphism.

Methods: We incorporated the mutation-induced changes in I_{Na} into the recently developed Fabbri-Severi model of a single human sinoatrial (SA) node cell. The threshold current of the Courtemanche-Ramirez-Nattel human right atrial cell model was used as a measure of atrial excitability.

Results: The E161K mutation increased the cycle length of the SA nodal cell by 54 ms. Under vagal tone, through the simulated presence of 20 nM acetylcholine, this increase raised to 191 ms, reducing the beating rate from 49 to 42 beats/min. The increase in cycle length was the result of a significant slowing of diastolic depolarization. The mutation-induced reduction in I_{Na} window current had reduced the contribution of the mutant component of I_{Na} to the net membrane current during diastole to effectively zero. Highly similar results were obtained with the H558R polymorphism. The E161K mutation increased the threshold stimulus current of the atrial cell by a factor of 2.3. The smaller shift in steady-state activation in case of the H558R polymorphism *per se* resulted in a smaller increase in threshold current, by a factor of 1.9, but in combination with the reduced availability of mutant I_{Na} channels through the −10-mV shift in steady-state inactivation, the threshold current was again increased by a factor of 2.3.

Conclusion: We conclude that the experimentally identified mutation-induced changes in I_{Na} 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.