Mechanism of Sinus Bradycardia in Carriers of the A414G Mutation in the HCN4 Gene

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**Background:** Heterozygous carriers of the A414G mutation in the HCN4 gene, which encodes the HCN4 protein, show moderate to severe sinus bradycardia. Tetramers of HCN4 subunits constitute the ion channels that conduct the cardiac hyperpolarization-activated ‘funny current’ ($I_f$), also known as the ‘pacemaker current’, which plays an important modulating role in the pacemaker activity of sinus node cells.

**Aim:** We assessed the mechanism by which the A414G mutation in HCN4 causes sinus bradycardia in the mutation carriers.

**Methods:** We carried out voltage clamp experiments on wild-type and heterozygous mutant HCN4 channels expressed in Chinese hamster ovary (CHO) cells at physiological temperature, using the amphothericin-perforated patch-clamp technique. We incorporated the experimentally observed mutation-induced changes in $I_f$ into the Fabbri-Severi model of a single human sinus node cell.

**Results:** The half-maximal activation voltage of the heterozygous mutant HCN4 current was 24 mV more negative than that of the wild-type current ($P<0.05$). The voltage dependence of the (de)activation time constant showed a similar shift, whereas no significant differences were observed in the slope factor of the activation curve, in the fully-activated current density, and in the reversal potential. In the Fabbri-Severi model, the $-24$ mV shift increased the cycle length from 813 to 1002 ms, corresponding with a 19% decrease in beating rate from 74 to 60 beats/min. Hyperpolarizing atrial load, simulated by incorporating an outward current with a conductance of 0.4–0.8 pS/pF and a reversal potential of $-80$ mV into the model sinus node cell, resulted in a 23–38% decrease in beating rate, indicating that the bradycardia was even more prominent in the presence of sinus node–atrial interactions.

**Conclusion:** We conclude that the experimentally identified mutation-induced changes in $I_f$ can explain the clinically observed sinus bradycardia in carriers of the A414G mutation in the HCN4 gene.