Functional Role of the *HCN4* Encoded 'Funny Current' in Human Sinus Node Cells

Arie O. Verkerk, Ronald Wilders*

Amsterdam University Medical Centers, location Academic Medical Center, University of Amsterdam
Amsterdam, The Netherlands

Background: Végh et al. recently reported patch clamp data on the voltage dependence of HCN4 channels expressed in human cardiomyocyte progenitor cells. The half-activation voltage of −86.7±2.1 mV was ≈10 mV less negative than previously observed by Verkerk et al. for the *HCN4* encoded hyperpolarization-activated 'funny current' (I_f) in isolated human sinus node cells. The time constant of (de)activation showed a similar ≈10 mV less negative voltage dependence.

Aim: We assessed the functional effect of a +10 mV shift in the voltage dependence of I_f kinetics.

Methods: We replaced the Verkerk et al. based kinetics of I_f in the Fabbri–Severi model of a single human sinus node cell with those reported by Végh et al.

Results: A +10 mV shift in its half-activation voltage *per se* resulted in a substantial increase in I_f, carrying 74 vs. 57% of the net diastolic depolarizing charge, and a 13% shortening of the cycle length from 813 to 710 ms. This effect was counteracted by a concomitant shift in the voltage dependence of the time constant, which caused a slower activation of I_f in the diastolic potential range. The resulting net effect was a 9.5% shortening of the cycle length from 813 to 736 ms, with I_f carrying 74% of the net diastolic charge. The adverse effect of the slowed activation was probably underestimated, because the experimentally observed apparent increase in the peak of the time constant vs. voltage relationship was not taken into account. With HCN4 based I_f kinetics, the model cell became more sensitive to autonomic modulation, as demonstrated by the 33 vs. 27% increase in beating rate in the simulated presence of 1 μM noradrenaline.

Conclusion: We conclude that the absolute value of the half-activation voltage of I_f may be less indicative of the functional role of I_f than commonly assumed.