An Engineering-Optimized Cardiac Pacemaker by Manipulating Na^+/Ca^+ Exchange and Na^+/K^+ Pumping

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Aims: Engineering a biological pacemaker could be created from ventricular myocytes by inhibiting the inward rectifier potassium channel current (I_{K1}) and augmenting the hyperpolarization-activated funny channel current (I_f), but there are some shortcomings such as unbalanced intracellular ionic concentrations and un-physiological pacing frequency. Previous studies have suggested that the expression of the I_{NaCa}-related genes was about 4-fold in cardiac pacemaking cells as compared other cell types. In addition, Na^+/K^+ pumping (I_{NaK}) may contribute to pump out extra Na^+ caused by the combined action of I_f in pacemaker cells. Thus, overexpressing I_{NaCa} and I_{NaK} may be helpful to improve the pacemaking ability of an engineered biological pacemaker.

Methods: A pacemaker model is constructed based on TP06 model by suppressing I_{K1} and incorporating I_f. Overexpression of I_{NaCa} and I_{NaK} is simulated by augmenting their channel maximal fluxes to investigate the modulating effect of the two channels on the pacemaking action potentials of the engineered pacemaker model.

Results: As compared with considerations of overexpressing I_{NaCa} or I_{NaK} alone, the cooperative action of overexpressing I_{NaCa} and I_{NaK} produced a more equilibrated intracellular ion concentrations and faster pacemaking action potentials. Under the integral action of augmented I_{NaCa} and I_{NaK}, the accumulation of the intracellular calcium concentration ($[Ca^{2+}]_i$) disappeared and the $[Ca^{2+}]_i$ became balanced at original low physiological level, which promoted the activation of L-type calcium current (I_{CaL}). Also, the flux of extra Na^+ by Na^+/K^+ pumping produced an increased I_f, promoting the depolarization of the pacemaking action potential. The augmented I_{NaCa} and I_{NaK} even altered I_f's property. Specifically, increasing I_f produced a faster pacemaking frequency which optimized the engineering pacemaking cell model.

Conclusion: The overexpression of I_{NaCa} and I_{NaK} balances the equilibrium of intracellular ionic concentrations thus enhances the pacemaking activity of an engineered biological pacemaker dramatically.