

Characterization of human embryonic stem cell-derived cardiomyocyte action potentials and channel conductances using a theoretical model.

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Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) can provide insights into the development of human myocardium and provide a powerful cellular system to investigate the electrical properties of human cardiomyocytes. In this study, we examined the action potentials (APs) of early developing hESC-CMs studied in spontaneously contracting EB outgrowths after 12-15 days of differentiation and modeled the channel conductances/activities responsible for the APs. Intracellular recordings using sharp KCl microelectrodes reveal cellular APs that are similar in basic form to those of early embryonic human cardiomyocytes. Comparison of the AP duration, AP upstroke slope and mean diastolic potential (MDP) show three distinct AP classes: nodal, embryonic-ventricular and embryonic-atrial. To gain a better understanding of the differences in channel activity underlying each AP class and to allow comparison to adult human cardiomyocytes, we used a modified version of a previously developed computational model of the adult cardiomyocyte. The main modification is the addition of a hyperpolarization-activated Na/K channel to represent the observed slow depolarization in diastole. The channels in this model are represented with a Hodgkin-Huxley formalism including parameters describing channel conductance, as well as inactivation and activation gating voltage and time constants. AP time courses are reproduced with this model by varying the various channel conductances (fast Na, rapid delayed rectifier K, etc.) In this manner the three differentiated hESC-CM classes have been characterized in terms of their relative channel conductances for the 12-16 day in culture developmental time point. Our results show that a more active background Na channel is required to adjust for the less polarized MDP seen in the recordings and general trends can be seen in both rapid delayed polarization and the L-type calcium conductances with respect to AP class and particular features of the AP shape.