In Silico Investigation of the CACNA1C N2091S mutation in Timothy Syndrome

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The CACNA1C-encoded L-type calcium channel transports Ca^{2+} into cardiac myocytes and is critical in the regulation of the cardiac action potential. Experimental studies demonstrated that CACNA1C-N2091S led to a gain-of-function in the L-type calcium current (I_{CaL}) linked to heritable Timothy Syndrome, but mechanisms by which the CACNA1C-N2091S mutation promotes and perpetuates ventricular fibrillation remain unclear. This study sought to investigate the proarrhythmic effects of CACNA1C-N2091S-induced I_{CaL}. Using a dynamic ventricular myocyte model incorporated with Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) signalling, we simulated I_{CaL}, APs, Ca^{2+} transients ($[Ca^{2+}]_i$) and sarcoplasmic reticulum (SR) calcium profiles ($[Ca^{2+}]_{SR}$) in three cell types (ENDO, MCELL and EPI). Effects of the CACNA1C-N2091S mutation on cell electrophysiology were quantified by changes in I_{CaL} density ($I_{CaL(max)}$), $[Ca^{2+}]_i$ amplitude ($[Ca^{2+}]_{i(max)}$), SR calcium content ($[Ca^{2+}]_{SR(max)}$), action potential duration (APD) and AP shape. It was shown that the CACNA1C-N2091S mutation increased $I_{CaL(max)}$, $[Ca^{2+}]_{i(max)}$, $[Ca^{2+}]_{SR(max)}$ and APD in three cell types. Compared with ENDO and EPI cells, MCELL cells with excessive prolongation of APD due to the CACNA1C-N2091S mutation facilitated inducibility of early afterdepolarization (EAD)-mediated triggered activity. And the different EAD inducibility among the three cell types can amplify the electrical difference and thereby dispersion of repolarization, increasing susceptibility to ventricular arrhythmias. Thus, the CACNA1C-N2091S mutation confers not only a trigger, but also a substrate for lethal ventricular arrhythmias.