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Investigation of Electrophysiological Mechanisms of Arrhythmogensis in Takotsubo Cardiomyopathy Using Human Induced Stem Cell Derived Cardiomyocytes

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In this study, cardiomyocytes derived from hiPS cells that were generated from human skin fibroblast cells of different healthy donors were used for investigating the ion channel functions and mechanisms underlying the arrhythmogenesis in Takotsubo cardiomyopathy (TTC).
The hiPSC-CMs possess all the channels that have been reported in native cardiomyocytes, including I_{Na}, $I_{Ca\text{-}L}$, I_f, I_{NCX}, I_{K1}, I_{to}, I_{Kr}, I_{Ks} I_{KATP}, $I_{K\text{-}pH}$, $I_{SK1\text{-}3}$, I_{SK4}. In addition, both the expression and currents of T-type Ca^{2+} channels, ACh-activated (KACh) and Na^+-activated (KNa) K^+ channels, volume-regulated (Cl-vol) and calcium-activated (Cl-Ca) Cl^- channels and TRPV channels were detected for the first time in hiPSC-CMs. All the detected ion currents except I_{K1}, I_{KACh}, I_{SK}, I_{KNa} and TRPV1 currents contribute to AP performance. Isoprenaline increased $I_{Ca\text{-}L}$, I_f, I_{Ks}, but reduced I_{Na}, I_{NCX}, without effect on I_{to}, I_{K1}, $I_{SK1\text{-}3}$, I_{KATP} I_{Kr}, I_{SK4}, I_{KNa}, $I_{Cl\text{-}Ca}$ and I_{TRPV1}. Carbachol alone showed no effect on ion channel currents. These data demonstrate that most ion channels, which are present in healthy or diseased cardiomyocytes, are functionally expressed in hiPSC-CMs with characterizations similar to that in native cardiomyocytes and are appropriate for studies on physiology or pathophysiology relating to ion channels in cardiomyocytes. Indeed, in hiPSC-CMs the electrophysiological phenotype (QTc-prolongation) in TTC was recapitulated, showing APD-prolongation in setting of stress (catecholamine excess). When hiPSC-CMs were treated by high concentration of isoprenaline (Iso), late I_{Na} was enhanced and I_{to} was suppressed and thus the action potential duration (APD) was prolonged. APD-prolongation at cellular level represents QT-prolongation at organ (ECG) level and may lead to arrhythmias. Iso elevated the production of reactive oxygen species (ROS). N-acetylcystein (1 mM), a ROS-blocker, abolished the effects of Iso on late I_{Na} and I_{to}. H_2O_2 (100 µM) mimicked Iso effects on late I_{Na} and I_{to}. These data indicate that the effects of Iso were mediated by ROS. Metoprolol (1 mM), a beta-blocker, prevented the effects of Iso on late I_{Na} and APD, confirming the adrenoceptor-dependent effects of Iso. Estradiol treatment prevented the APD-prolongation, attenuated the enhancement of I_{Na}, diminished the reduction of I_{to}, suppressed ROS-production induced by Iso and reduced the expression levels of adrenoceptors, suggesting protective effects of estragon against toxic effects of catecholamine. These data indicated that: (1) High concentration catecholamine elevated ROS production and caused ion channel dysfunctions resulting APD-prolongation; (2) Estradiol exerted protective effects against catecholamine excess and hence reduction in estrogen level may increase the risk of acquired long QT syndrome in TTC.
In conclusion, this study demonstrates that the ion channels that exist in mature cardiomyocytes are also present in hiPSC-CMs with similarities or differences in some aspects; Catecholamine excess may increase ROS production; ROS can enhance late I_{Na} and inhibit I_{to} and in turn prolong APD; APD-prolongation leads to long-QT, which may cause arrhythmias; Estrogen may reduce the sensitivity of cardiomyocytes to catecholamine via reducing adrenoceptor expression. This study also suggests that β-blocker, ROS-blocker, late sodium channel blocker and I_{to} activator may be potential alternatives for the treatment of arrhythmias induced by catecholamine excess. Finally, the novel data from this study may provide useful information for future studies regarding ion channels in hiPSC-CMs and modeling heart diseases using hiPSC-CMs.