Intercalated Disc-Associated Protein mXinα Influences Surface Expression of I_{to} and I_{K1} Currents in Ventricular Myocytes

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Mouse Xinα (mXinα) encodes a Xin repeat-containing, actin-binding protein localized to the intercalated disc (ICD). Ablation of mXinα progressively leads to disrupted ICD structure, cardiac hypertrophy and cardiomyopathy with conduction defects during adulthood. Such conduction defects could be due to ICD structural defects and/or cell electrophysiological property changes. Here, we showed that despite the normal ICD structure, juvenile mXinα-null cardiomyocytes (from 3–4-week-old mice) exhibited a significant reduction in the I_{to}, similar to adult mutant cells. Juvenile but not adult mutant cardiomyocytes also had a significant reduction in the I_{K1} on hyperpolarization. In contrast, the mutant adult ventricular myocytes had a significant reduction in the I_{K1} on hyperpolarization. These together could account for the prolongation of APD and developing EAD observed in juvenile mXinα-null cells. Interestingly, juvenile mXinα-null cardiomyocytes had a notable decrease in the amplitude of intracellular Ca^{2+} transient and no change in the I_{Ca,L}, suggesting that the prolonged APD did not promote an increase in [Ca^{2+}], for cardiac hypertrophy. Juvenile mXinα-null ventricles had reduced levels of membrane-associated KChIP2, an auxiliary subunit of I_{to}, and filamin, an actin cross-linking protein. We further showed that mXinα interacted with both proteins, providing a novel mechanism for I_{to} surface expression.

Keywords: juvenile vs. adult, intercalated disc, transient outward K+ current & inward rectifier K+ current