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ORIGINAL ARTICLE

Activation of TRPC (Transient Receptor Potential Canonical) Channel Currents in Iron Overloaded Cardiac Myocytes

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BACKGROUND: Arrhythmias and heart failure are common cardiac complications leading to substantial morbidity and mortality in patients with hemochromatosis, yet mechanistic insights remain incomplete. We investigated the effects of iron (Fe) on electrophysiological properties and intracellular Ca^{2+} (Ca^{2+}_i) handling in mouse left ventricular cardiomyocytes.

METHODS: Cardiomyocytes were isolated from the left ventricle of mouse hearts and were superfused with Fe^{3+}/8-hydroxyquinoline complex (5–100 μM). Membrane potential and ionic currents including TRPC (transient receptor potential canonical) were recorded using the patch-clamp technique. Ca^{2+}_i was evaluated by using Fluo-4. Cell contraction was measured with a video-based edge detection system. The role of TRPCs in the genesis of arrhythmias was also investigated by using a mathematical model of a mouse ventricular myocyte with the incorporation of the TRPC component.

RESULTS: We observed prolongation of the action potential duration and induction of early and delayed afterdepolarizations in myocytes superfused with 15 μmol/L Fe^{3+}/8-hydroxyquinoline complex. Iron treatment decreased the peak amplitude of the L-type Ca^{2+} current and total K^+ current, altered Ca^{2+}_i dynamics, and decreased cell contractility. During the final phase of Fe treatment, sustained Ca^{2+}_i waves and repolarization failure occurred and ventricular cells became unexcitable. Gadolinium abolished Ca^{2+}_i waves and restored the resting membrane potential to the normal range. The involvement of TRPC activation was confirmed by TRPC channel current recordings in the absence or presence of functional TRPC channel antibodies. Computer modeling captured the same action potential and Ca^{2+}_i dynamics and provided additional mechanistic insights.

CONCLUSIONS: We conclude that iron overload induces cardiac dysfunction that is associated with TRPC channel activation and alterations in membrane potential and Ca^{2+}_i dynamics.

Key Words: action potential ■ electrophysiology ■ hemochromatosis ■ iron ■ membrane potential

Nonstandard Abbreviations and Acronyms

$[Ca^{2+}]_i$	intracellular calcium ion concentration