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Intracellular $[Na^+]_i$ modulates synergism between Na^+/Ca^{2+} exchanger and Ca^{2+} current in cardiac excitation-contraction coupling during an action potential

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Location: Clark 110

Podcast available after seminar

Abstract

Contraction of cardiac myocytes is initiated by Ca^{2+} influx through L-type Ca channels, which induces Ca^{2+} release from the sarcoplasmic reticulum (SR). The contribution of Ca^{2+} entry via the Na^+/Ca^{2+} exchanger (NCX) to triggering Ca^{2+} release during excitation-contraction coupling (ECC) during an action potential (AP) remains uncertain. In order to isolate the contribution of NCX to SR Ca^{2+} release, independent of its effects on SR Ca^{2+} load, Ca^{2+} release was determined by recording Ca^{2+} spikes using confocal microscopy of patch-clamped rat ventricular myocytes with $[Ca^{2+}]_i$ fixed at 150 nmol/L. In response to AP clamps, normalized Ca^{2+} spike amplitudes ($*F/F_0$) increased ($P < 0.005$) sigmoidally from 0.40 ± 0.08 to 0.80 ± 0.06 as $[Na^+]_i$ was elevated from 0 to 20 mmol/L with an EC_{50} of 9.08 ± 0.97 mmol/L. The $[Na^+]_i$ dependent enhancement of SR Ca^{2+} release was independent of I_{Na} or SR Ca^{2+} load. However, NCX inhibition using either 5 μ mol/L KB-R7943 or 30 μ mol/L XIP reduced ($P < 0.05$) $*F/F_0$ amplitudes in myocytes with 20 mmol/L $[Na^+]_i$ but not with 5 mmol/L $[Na^+]_i$. Since $I_{Ca,L}$ inhibition with 50 mmol/L Cd^{2+} totally abolished Ca^{2+} spikes, our results demonstrate that, during a cardiac AP at elevated $[Na^+]_i$, NCX enhances SR Ca^{2+} release, by synergistically increasing the efficiency of $I_{Ca,L}$ -mediated ECC. Additionally, the slope of the initial repolarization phase of the cardiac AP is a key regulator of ECC. We hypothesize that this synergy between NCX and $I_{Ca,L}$ is responsible for AP dependent modulation of cardiac ECC. In voltage-clamped rat ventricular myocytes, we measured Ca^{2+} spikes triggered by a family of APs with varying slopes of initial repolarization. In myocytes containing 20 mmol/L $[Na^+]_i$, $*F/F_0$ displayed a biphasic relationship with AP duration at 50% repolarization (APD_{50}), rising initially then decreasing as APD_{50} of the triggering AP increased from 4 to 52 ms. Maximal Ca^{2+} release flux was achieved when APD_{50} was 16 ms ($*F/F_0 = 0.77 \pm 0.06$, $n = 17$). In the presence of XIP the APD -dependence of Ca^{2+}

+ spikes

0.60 ± 0.06 at 16 ms APD₅₀. In myocytes containing 5 mmol/L $[Na^+]_i$, the APD-dependence was also blunted ($*F/F_0 = 0.53 \pm 0.06$, at 9 ms APD₅₀, $n=16$) and was unaffected by XIP. We conclude that the biphasic enhancement of SR Ca^{2+} release with prolongation of APD is achieved through functional synergy between NCX and L-type Ca^{2+} channel trigger sources of CICR.