

The mechanism of injury-induced $[Ca^{2+}]_i$ oscillations in the endothelium of excised rat aorta

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Endothelial injury is the primary event that leads to a variety of severe vascular disorders. The signal transduction pathway which drives the subsequent healing process is far from being fully elucidated. Mechanical injury elicits a Ca^{2+} response in the endothelium of intact rat aorta, which comprises an initial Ca^{2+} release from inositol-1,4,5-trisphosphate-sensitive (IP₃Rs) stores followed by a long-lasting decay phase due to Ca^{2+} entry through uncoupled connexons. In a minor fraction of cells, the Ca^{2+} signal adopts an oscillatory pattern whose molecular underpinnings are yet to be elucidated. In the light of the role played by repetitive Ca^{2+} spikes in regulating tissue regeneration, the present study aims at elucidating the mechanisms underlying injury-induced Ca^{2+} oscillations. The repetitive Ca^{2+} signal reversibly ceased upon removal of extracellular Ca^{2+} or addition of the inorganic cations, La^{3+} and Ni^{2+} . Moreover, the spiking response was abolished by the gap-junction blockers, heptanol and 18 beta-glycyrrhetic acid and by interfering with the Ca^{2+} entry-mode mode of the Na^{+}/Ca^{2+} exchanger (NCX). The InsP₃-producing agonist, ATP, resumed Ca^{2+} oscillations in silent cells, while the phospholipase C inhibitor, U73122, inhibited the oscillatory signal. The latter was also prevented by the SERCA inhibitors, thapsigargin and cyclopiazonic acid. These data show that injury-induced $[Ca^{2+}]_i$ oscillations require the coordinated interplay between NCX-mediated Ca^{2+} entry and InsP₃-dependent Ca^{2+} release. Besides directly gating Ca^{2+} inflow, uncoupled connexons might let Na^{+} into the cells and stimulate Ca^{2+} entry through NCX by increasing submembranal Na^{+} levels.

Keywords: rat aorta, endothelial injury, Ca^{2+} oscillations, gap junction blockers, $Na^{+}-Ca^{2+}$ exchanger, InsP₃ receptors