A New Beginning for Normal Automaticity of the Cardiac Pacemaker

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ABSTRACT: Earlier studies of the initiating event of normal automaticity of the heart's pacemaker cells, inspired by classical quantitative membrane theory, had focused upon ion channel currents that determine the maximum diastolic potential and the early phase of the spontaneous diastolic depolarization (DD). These early DD events (e.g., changes in activation states of I_k, I_f,) occur in response to membrane potential changes during the action potential (AP), and are essentially related to membrane recovery from the prior AP. More recent studies delineate a "new beginning" of pacemaker initiation, effected by events that occur during the late DD. Regardless of size, isolated rabbit sinoatrial cells (SANC) exhibit intense RyR, NCX1 and SERCA2 labeling and dense submembrane NCX/RyR colocalization. Spontaneous stochastic, but roughly periodic, Local subsarcolemmal ryanodine receptor-mediated Ca^{2+} Releases (LCR) generate inward currents during the late DD via the Na/Ca exchanger (NCX), producing V_m fluctuations with amplitudes of approximately 2 mV. The ensemble of NCX current fluctuations imparts a nonlinear exponentially rising phase to the later part of the DD, while suppression of I_f affects only the early linear DD. LCR periodicity is precisely controlled by the kinetics of SR Ca^{2+} cycling, which in turn is physiologically regulated by the status of protein-kinase A-dependent phosphorylation of Ca^{2+} cycling proteins. Maneuvers that alter LCR timing (ryanodine, BAPTA, or isoproterenol) produce corresponding changes in V_m fluctuations and nonlinear DD component amplitude. Furthermore, the late DD V_m fluctuation response which is evoked by these maneuvers is tightly correlated with the concurrent induced changes in spontaneous beating rate. These data, supported by numerical modeling, indicate that the timing and amplitude of LCR/ I_{NCX}-generated events control the timing and amplitude of the nonlinear terminal DD, therefore ultimately control the chronotropic state by determining the timing of the activation of the ensemble surface membrane ion channels that generate the next AP. LCR/NCX-initiated ignition of the membrane potential during the late DD can therefore be construed as the "beginning step" of normal pacemaker cell automaticity.

KEYWORDS: cardiac pacemaker, automaticity, calcium, ryanodine receptor, sodium calcium exchanger

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