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Review

'Ca^{2+}-induced Ca^{2+} entry' or how the L-type Ca^{2+} channel remodels its own signalling pathway in cardiac cells

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Abstract

The adjustment of Ca^{2+} entry in cardiac cells is critical to the generation of the force necessary for the myocardium to meet the physiological needs of the body. In this review, we present the concept that Ca^{2+} can promote its own entry through Ca^{2+} channels by different mechanisms. We refer to it under the general term of '*Ca^{2+}-induced Ca^{2+} entry*' (CICE). We review short-term mechanisms (usually termed *facilitation*) that involve a stimulating effect of Ca^{2+} on the L-type Ca^{2+} current ($I_{Ca\text{-}L}$) amplitude (positive *staircase*) or a lessening of Ca^{2+}-dependent inactivation of $I_{Ca\text{-}L}$. This latter effect is related to the amount of Ca^{2+} released by ryanodine receptors (RyR2) of the sarcoplasmic reticulum (SR). Both effects are involved in the control of action potential (AP) duration. We also describe a long-term mechanism based on Ca^{2+}-dependent down-regulation of the Kv4.2 gene controlling functional expression of the repolarizing transient outward K^+ current (I_{to}) and, thereby, AP duration. This mechanism, which might occur very early during the onset of hypertrophy, enhances Ca^{2+} entry by maintaining Ca^{2+} channel activation during prolonged AP. Both Ca^{2+}-dependent facilitation and Ca^{2+}-dependent down-regulation of I_{to} expression favour AP prolongation and, thereby, promote sustained voltage-gated Ca^{2+} entry used to enhance excitation–contraction (EC) coupling (with no change in the density of Ca^{2+} channels per se). These self-maintaining mechanisms of Ca^{2+} entry have significant functions in remodelling Ca^{2+} signalling during the

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cardiac AP. They might support a prominent role of Ca^{2+} channels in the establishment and progression of abnormal Ca^{2+} signalling during cardiac hypertrophy and congestive heart failure.

Keywords: Ca^{2+} channel facilitation; Positive staircase; Transient outward K^+ current; Excitation–Transcription coupling

Contents

1. Introduction

Ca^{2+} is a cation of critical significance for cell life, notably in heart physiology. The key role of Ca^{2+} in maintaining cardiac contraction was originally demonstrated by the British physiologist Sidney Ringer who first observed the dependence of isolated frog heart's contractility upon the presence of extracellular Ca^{2+} (Ringer, 1883). Ca^{2+} ions can, easily and very rapidly (sub-millisecond time scale), cross the sarcolemmal membrane to generate intracellular Ca^{2+} signals. This property is based on the electrochemical gradient of Ca^{2+} ions between the extracellular (millimolar range) and the intracellular compartments. In resting cells, intracellular free ionized Ca^{2+} is maintained at low concentration (nanomolar range) by mechanisms that prevent its entry (typically via the closing of voltage-gated Ca^{2+} channels), enable its extrusion (typically via the Na^+/Ca^{2+} exchanger), and induce its storage (typically via the Ca^{2+} ATPase SERCA2a) in intracellular compartments (sarcoplasmic reticulum, SR) (Bers, 2000).

Ca^{2+} entry is mediated mainly by the cardiac L-type Ca^{2+} channel, which is central to the initiation of excitation–contraction (EC) coupling via Ca^{2+}-induced Ca^{2+} release (CICR) from the SR. Regulation of the L-type Ca^{2+} current ($I_{Ca\text{-}L}$) has, therefore, profound physiological significance. This can be achieved in many ways, including modulation by various hormones and neurotransmitters, intracellular messengers and phosphorylation pathways. One immediate effect