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Review article

Integration of calcium with the signaling network in cardiac myocytes

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Abstract

Calcium has evolved as global intracellular messenger for signal transduction in the millisecond time range by reversibly binding to calcium-sensing proteins. In the cardiomyocyte, ion pumps, ion exchangers and channels keep the cytoplasmic calcium level at rest around ~100 nM which is more than 10,000-fold lower than outside the cell. Intracellularly, calcium is mainly stored in the sarcoplasmic reticulum, which comprises the bulk of calcium available for the heartbeat. Regulation of cardiac function including contractility and energy production relies on a three-tiered control system, (i) immediate and fast feedback in response to mechanical load on a beat-to-beat basis (Frank-Starling relation), (ii) more sustained regulation involving transmitters and hormones as primary messengers, and (iii) long-term adaptation by changes in the gene expression profile. Calcium signaling over largely different time scales requires its integration with the protein kinase signaling network which is governed by G-protein-coupled receptors, growth factor and cytokine receptors at the surface membrane. Short-term regulation is dominated by the β-adrenergic system, while long-term regulation with phenotypic remodeling depends on sustained signaling by growth factors, cytokines and calcium. Mechanisms and new developments in intracellular calcium handling and its interrelation with the MAPK signaling pathways are discussed in detail.

Keywords: Calcium signaling; Intracellular signaling; Cardiac remodeling; Mitochondrial calcium regulation; MAPK signaling; Adrenergic signaling

Contents

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1. Introduction

Intracellular signaling coordinates life sustaining cellular processes as diverse as growth, differentiation, maintenance of specific cell functions, energy production to match demand, protective responses to various types of extracellular stressors (e.g. mechanical stretch or hypoxia), and, if the rescue operation fails, even energy consuming programmed death by apoptosis. Stimuli for these various processes reach the cell in the form of extracellular primary messengers like transmitters and hormones (e.g. catecholamines, angiotensin-II, endothelin, growth factors, cell mediators) via the blood. In the case of excitable cells such as cardiomyocytes, the stimulus for contraction, a fast process that takes place in a fraction of a second, induces depolarisation of the resting membrane potential (around −80 mV), which involves a series of ionic fluxes through the membrane including entry of Ca^{2+} to the cytoplasm. The Ca^{2+} ion was shown to serve as intracellular second messenger controlling fast processes such as contraction.

On the other hand, myocyte maintenance and hypertrophic remodeling represent long-lasting processes under the control of distinct intracellular signaling pathways that have been defined within the past decades [1–4]. These signaling cascades primarily relay to two broad classes of surface membrane receptors, the G-protein coupled receptors with seven trans-membrane segments (GPCRs) and the receptor components with one membrane-inserted segment displaying intrinsic enzyme activity, receptor tyrosine kinases (RTK) or receptor Ser/Thr kinases (RSTK). Signal transduction in these cascades is predominantly effected, step by step, via reversible phosphorylation reactions [1,3]. However, Ca^{2+} plays a decisive role not only at multiple steps in the receptor-dependent cascades but in many instances constitutes the ultimate signal transducer in the chain, which is responsible for the cellular response.

2. Aim of this review

We focus here on how Ca^{2+} as the major intracellular messenger is integrated into the general signaling network and how the different pathways ultimately affect the Ca^{2+}-modulated cellular responses. This may be justified by the fact that research in the two fields of Ca^{2+} signaling and receptor-dependent cascading does not entirely overlap. Since our approach covers a wide area of research, reviews – where the reader may find the primary literature – are often cited.

By selecting from the large body of literature, we have constructed a series of schematic diagrams integrating major aspects of intracellular signaling in order to visualize the complexity at different levels (Figs. 1–3). Fig. 1 displays the