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Review article

Emerging roles of inositol 1,4,5-trisphosphate signaling in cardiac myocytes

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Abstract

Inositol 1,4,5-trisphosphate (IP_3) is a ubiquitous intracellular messenger regulating diverse functions in almost all mammalian cell types. It is generated by membrane receptors that couple to phospholipase C (PLC), an enzyme which liberates IP_3 from phosphatidylinositol 4,5-bisphosphate (PIP_2). The major action of IP_3, which is hydrophilic and thus translocates from the membrane into the cytoplasm, is to induce Ca^{2+} release from endogenous stores through IP_3 receptors (IP_3Rs). Cardiac excitation–contraction coupling relies largely on ryanodine receptor (RyR)-induced Ca^{2+} release from the sarcoplasmic reticulum. Myocytes express a significantly larger number of RyRs compared to IP_3Rs (~100:1), and furthermore they experience substantial fluxes of Ca^{2+} with each heartbeat. Therefore, the role of IP_3 and IP_3-mediated Ca^{2+} signaling in cardiac myocytes has long been enigmatic. Recent evidence, however, indicates that despite their paucity cardiac IP_3Rs may play crucial roles in regulating diverse cardiac functions. Strategic localization of IP_3Rs in cytoplasmic compartments and the nucleus enables them to participate in subsarcolemmal, bulk cytoplasmic and nuclear Ca^{2+} signaling in embryonic stem cell-derived and neonatal cardiomyocytes, and in adult cardiac myocytes from the atria and ventricles. Intriguingly, expression of both IP_3Rs and membrane receptors that couple to PLC/IP_3 signaling is altered in cardiac disease such as atrial fibrillation or heart failure, suggesting the involvement of IP_3 signaling in the pathology of these diseases. Thus, IP_3 exerts important physiological and pathological functions in the heart, ranging from the regulation of pacemaking, excitation–contraction and excitation–transcription coupling to the initiation and/or progression of arrhythmias, hypertrophy and heart failure.

Keywords: Inositol 1,4,5-trisphosphate; Cardiac myocyte; Calcium; Inotropy; Arrhythmias; Nucleus; Hypertrophy

Contents

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1. The discovery of IP_3

A quarter of a century ago it was shown that D-*myo* inositol 1,4,5-trisphosphate (IP_3) releases Ca^{2+} from a non-mitochondrial internal Ca^{2+} store [1]. Since this hallmark discovery, IP_3 has emerged as a ubiquitous intracellular messenger, releasing Ca^{2+} from stores through activation of IP_3 receptors (IP_3Rs) in almost all eukaryotic cells. The major IP_3-sensitive intracellular Ca^{2+} store is the endoplasmic reticulum. However, IP_3 has also been shown to release Ca^{2+} stored in other compartments, such as the Golgi and the nuclear envelope [2]. In addition, IP_3Rs are present on the plasma membrane of some cell types, where they can gate Ca^{2+} influx [3]. A crucial role for IP_3-dependent Ca^{2+} release has been demonstrated in many mammalian cell types, ranging from tiny platelets, where it initiates blood clotting, to the impressive dendritic trees of cerebellar Purkinje neurons, where it is involved in the regulation of motor function. In the cardiovascular system, IP_3-induced Ca^{2+} release from the sarcoplasmic reticulum (SR) plays a key role in pharmaco-mechanical coupling in smooth muscle cells of the vasculature, and thus in the regulation of peripheral resistance and blood pressure. Despite being recognized as a potential messenger in cardiac myocytes nearly two decades ago, the role of IP_3 has been enigmatic. However, a number of recent reports have begun to unravel the physiological and potentially pathological actions of IP_3 within the heart.

2. The ABC of IP_3: where does it come from and where does it go?

IP_3 is generated by hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) through phosphoinositide-specific phospholipase C (PLC). PIP_2 is a relatively minor phospholipid (~1% of total anionic phospholipids), but it is the main polyphosphoinositide in the sarcolemma. Its concentration in myocardium is in the range of 10–30 μM or 150–450 pmol/mg protein [4,5]. PIP_2 itself serves important signaling functions, including the regulation of ion channels and transporters and the anchoring of cytoskeletal proteins at the membrane [6,7]. Furthermore, it is the precursor of phosphatidylinositol 3,4,5-trisphosphate (PIP_3), a phosphoinositide involved in cell signaling. There are at least 13 phosphoinositide-specific PLC isoforms grouped into six subfamilies: β, γ, δ, ε, η and ζ [8,9]. Members of the β, γ, δ and ε subfamilies are expressed in cardiac myocytes. PLCs may be activated by heptahelical G protein-coupled receptors (PLCβ), receptor tyrosine kinases (PLCγ), PIP_2 and Ca^{2+} (PLCδ) or Ras (PLCε). Consequently, many transmitters, neurohormonal factors, hormones and other stimuli (e.g. stretch) may increase IP_3 concentration and activate IP_3-induced Ca^{2+} release in cardiac myocytes downstream of PLC activation. Upon stimulation, intracellular IP_3, or inositol phosphate concentration in general, has been shown to increase by a factor of >12 [10]. However, it should be pointed out that most of these data were determined from assays of measuring total inositol phosphate accumulation over time (in the presence of the inositol monophosphatase inhibitor Li^+). Such measurements do not reflect the *in vivo* steady-state IP_3 increase, which is likely to be quite modest. Recently, the concentration of free IP_3 was estimated directly using a novel FRET-based biosensor. Following maximal stimulation of α-adrenergic and endothelin receptors, free IP_3 in cardiac myocytes increased to ~30 nM [11]. While such biosensors are useful for detecting genuine increases in IP_3 concentration, they are less helpful in revealing the kinetics of IP_3 turnover, since binding of IP_3 to the probe buffers the molecule and protects it from hydrolyzing enzymes. Based on modeling studies, it was estimated that stimulation of atrial myocytes with endothelin transiently increases IP_3 concentration from a basal value of ~15 nM to a maximal value of ~35 nM within ~400 s, after which the IP_3 level gradually declines and returns to baseline within tens of minutes [12]. A note of caution as to the quantitative results obtained with isolated myocytes is warranted though, since careful studies indicate that PIP_2 and inositol phosphate levels drop dramatically during the isolation procedure [13,14].

Because IP_3 is hydrophilic, it translocates from the sarcolemma to the cytoplasm upon formation from PIP_2. The main cytoplasmic target of IP_3 is IP_3Rs in the membrane of the ER/SR. There are three IP_3R isoforms, denoted type 1, type 2 and type 3. Current evidence suggests that the heart expresses all three IP_3R isoforms, although there is some inconsistency in the literature regarding their relative ratios in different cardiac cells. It has been proposed that type 1 IP_3Rs are dominant in human atrial and rat Purkinje myocytes [15,16], whereas atrial and ventricular myocytes from most other animal species express predominantly type 2 IP_3R and, to a lesser extent, type 3 IP_3R (e.g. [17,18]). Overall, the majority of studies have concluded that the most prevalent IP_3R isoform within contractile cardiomyocytes is type 2 (see Table 1). The few reports describing