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Ins(1,4,5)P_3 receptors and inositol phosphates in the heart—evolutionary artefacts or active signal transducers?

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Abstract

The generation of the second messenger inositol 1,4,5-trisphosphate (Ins(1,4,5)P_3) and its associated release of Ca^{2+} from internal stores is a highly conserved module in intracellular signaling from *Drosophila* to mammals. Many cell types, often nonexcitable cells, depend on this pathway to couple external signals to intracellular Ca^{2+} release. However, despite the presence of the requisite Ins(1,4,5)P_3 signaling machinery, excitable cells such as cardiac myocytes employ a robust alternate system of intracellular Ca^{2+} release, namely, a coupled system of Ca^{2+} influx, followed by Ca^{2+} release via the IP_3R-related ryanodine receptors. In these systems, Ins(1,4,5)P_3 signaling pathways appear to be largely dormant. In this review, we consider the general features of inositol phosphate (InsP) responses in cardiac myocytes and the molecules mediating these responses. The spatial localization of Ins(1,4,5)P_3 generation and Ins(1,4,5)P_3 receptor (IP_3Rs) is likely of key importance, and we examine the state of knowledge in atrial, ventricular, and Purkinje myocytes. Several studies have implicated Ins(1,4,5)P_3 generation in both arrhythmogenic and hypertrophic responses, and possible mechanisms involving Ins(1,4,5)P_3 are discussed. While Ins(1,4,5)P_3 is unlikely to be a key player in cardiac excitation–contraction (EC) coupling, its potential role in an alternate Ca^{2+} release system to signal changes in gene transcription warrants further investigation. Such studies will help to determine whether cardiac Ins(1,4,5)P_3 generation represents a vestigial pathway or plays an active role in cardiac signaling.

Keywords: Inositol phosphates; Phospholipase C; Arrhythmia; Hypertrophy

Abbreviations: α_1-AR, α_1-adrenergic receptor; ANP, atrial natriuretic factor; APD, action potential duration; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CnA, calcineurin A; DAG, *sn*-1,2-diacylglycerol; EC, excitation–contraction; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; GEF, guanyl nucleotide exchange factor; GPCR, G protein-coupled receptor; GSK, glycogen synthase kinase; HDAC, histone deacetylase; INPP, inositol polyphosphate 1-phosphatase; InsP, inositol phosphate; Ins(1,4,5)P_3, inositol(1,4,5)trisphosphate; Ins(1,4)P_2, inositol(1,4)bisphosphate; IP_3R, Ins(1,4,5)P_3 receptor; JNK, c-Jun-NH_2-terminal kinase; MAPK, mitogen-activated protein kinase; MEF2, myocyte enhancer factor 2; MLC, myosin light chain; NFAT, nuclear factor of activated T-cells; PLC, phospholipase C; PtdInsP, phosphatidylinositol(4)monophosphate; PtdInsP_2, phosphatidylinositol(4,5)bisphosphate; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase; SRF, serum response factor.

Contents

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1. Introduction

The heart is a specialized organ. Its most obvious function is to contract rhythmically and in a controlled manner, but it must also be able to increase in size to accommodate changes during development or when faced with a pathological stimulus. Both contractility and growth are influenced by extracellular factors that activate cell surface receptors and initiate signaling responses within cardiomyocytes. It is clearly of the utmost importance that the different responses are correctly encoded; yet, both contractility and growth utilize a signaling pathway in common, which is the shuttling of Ca^{2+}. This review will consider the potential role of inositol(1,4,5)trisphosphate ($Ins(1,4,5)P_3$) and its receptors (IP_3Rs) in the control of cardiac Ca^{2+} and subsequent downstream responses.

2. Cardiac excitation–contraction coupling

The regulation of contractility is orchestrated by a spatially defined program of ion channels and exchangers that accurately control the entry and release of Ca^{2+} into the cell and from the sarcoplasmic reticulum (SR). Despite the fact that the process centers primarily around Ca^{2+}, there does not appear to be a substantial role for $Ins(1,4,5)P_3$ and its associated Ca^{2+} release in regulating beat-to-beat contraction. In heart, the control of Ca^{2+} release and, therefore, the regulation of contractility is predominantly achieved via the electrical activity of the sarcolemma. The cardiac action potential is initiated by depolarization of the sarcolemma and sustained in the plateau phase by the activation of voltage-gated L-type Ca^{2+} channels ($I_{Ca,L}$). Ca^{2+} entry via these channels causes Ca^{2+} release from the SR mediated by ryanodine receptors, the most abundant intracellular Ca^{2+} channels in cardiomyocytes, in a process termed Ca^{2+}-induced Ca^{2+} release. The free Ca^{2+} so generated increases the contraction of the myofilaments via its interaction with troponin C and subsequent enhancement of the actin–myosin interaction (Williams et al., 1992; Minamikawa et al., 1997). The removal of Ca^{2+} from the cytosol is achieved by several mechanisms, including SR uptake via sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA; Giordano et al., 1997) and extrusion over the sarcolemma via the Na^+/Ca^{2+} exchanger (Hilgemann, 2004). It is noteworthy that none of these processes involves $Ins(1,4,5)P_3$, and factors that activate phospholipase C (PLC), such as α_1-adrenergic agonists and endothelin, are not considered major regulators of cardiac function under physiological conditions (Jacobsen et al., 1997; Woodcock et al., 1999). This raises questions as to why $Ins(1,4,5)P_3$-regulated Ca^{2+} responses do not make a more substantial contribution to excitation–contraction (EC) coupling under physiological conditions.

3. Inositol(1,4,5)trisphosphate-mediated Ca^{2+} responses—a general model

$Ins(1,4,5)P_3$ is a major regulator of Ca^{2+}-related responses in nonexcitable cells, and it is worthwhile to consider how this is achieved. $Ins(1,4,5)P_3$ is generated from the precursor lipid $PtdIns(4,5)P_2$ by phospholipase C (PLC) cleavage. $PtdIns(4,5)P_2$ itself is formed by the sequential phosphorylation of PtdIns at the 4′ and 5′ positions and is generally replenished after PLC cleavage. There are 4 classes of PLC enzymes (β, γ, δ, and ε) expressed widely (Rhee, 2001), as well as a novel isoform (ζ) involved in fertilization (Saunders et al., 2002). PLCγ isoforms are activated by receptors for certain growth factors and cytokines following tyrosine phosphorylation and plasma membrane localization mediated by SH2 domain interactions. PLCβ isoforms are regulated by the activated α subunits of members of the Gq class of heterotrimeric G proteins or, in some cases, by βγ subunits from Gi family members. In either case, PLCβ activation reflects the binding of ligand to specific 7-transmembrane receptors. PLCδ lacks several of the regulatory modules found on the other classes of PLC, and its activation may depend solely on increases in Ca^{2+} concentration in its vicinity. PLCε is a newly discovered class of PLC, present in the heart, which contains RasGEF and Ras-activated domains in addition to the conserved catalytic and Ca^{2+}-binding C2 domains characteristic of other PLC isoforms and which may also be activated by the G_{12} class of heterotrimeric G proteins (Lopez et al., 2001; Song et al., 2001, 2002).

PLC activation generates $Ins(1,4,5)P_3$, which is thus released from the membrane to interact with specific $Ins(1,4,5)P_3$ receptors (IP_3Rs). IP_3Rs are intracellular Ca^{2+} channels expressed on the endoplasmic reticulum (ER) Ca^{2+} stores (Fig. 1). A current operational definition of IP_3Rs is that they are intracellular Ca^{2+} release channels that respond to changes in Ca^{2+} through a process of Ca^{2+}-induced Ca^{2+} release, in a manner akin to ryanodine receptors, but which