Calcium and IP3 dynamics in cardiac myocytes: experimental and computational perspectives and approaches

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Calcium plays a crucial role in excitation-contraction coupling (ECC), but it is also a pivotal second messenger activating Ca2+-dependent transcription factors in a process termed excitation-transcription coupling (ETC). Evidence accumulated over the past decade indicates a pivotal role of inositol 1,4,5-trisphosphate receptor (IP3R)-mediated Ca2+ release in the regulation of cytosolic and nuclear Ca2+ signals. IP3 is generated by stimulation of plasma membrane receptors that couple to phospholipase C (PLC), liberating IP3 from phosphatidylinositol 4,5-bisphosphate (PIP2). An intriguing aspect of IP3 signaling is the presence of the entire PIP2-PLC-IP3 signaling cascade as well as the presence of IP3Rs at the inner and outer membranes of the nuclear envelope (NE) which functions as a Ca2+ store. The observation that the nucleus is surrounded by its own putative Ca2+ store raises the possibility that nuclear IP3-dependent Ca2+ release plays a critical role in ETC. This provides a potential mechanism of regulation that acts locally and autonomously from the global cytosolic Ca2+ signal underlying ECC. Moreover, there is evidence that: (i) the sarcoplasmic reticulum (SR) and NE are a single contiguous Ca2+ store; (ii) the nuclear pore complex is the major gateway for Ca2+ and macromolecules to pass between the cytosol and the nucleoplasm; (iii) the inner membrane of the NE hosts key Ca2+ handling proteins including the Na+/Ca2+ exchanger (NCX)/GM1 complex, ryanodine receptors (RyRs), nicotinic acid adenine dinucleotide phosphate receptors (NAADPRs), Na+/K+ ATPase, and Na+/H+ exchanger. Thus, it appears that the nucleus represents a Ca2+ signaling domain equipped with its own ion channels and transporters that allow for complex local Ca2+ signals. Many experimental and modeling approaches have been used for the study of intracellular Ca2+ signaling but the key to the understanding of the dual role of Ca2+ mediating ECC and ECT lays in quantitative differences of local [Ca2+] in the nuclear and cytosolic compartment. In this review, we discuss the state of knowledge regarding the origin and the physiological implications of nuclear Ca2+ transients in different cardiac cell types (adult atrial and ventricular myocytes) as well as experimental and mathematical approaches to study Ca2+ and IP3 signaling in the cytosol and nucleus. In particular, we focus on the concept that highly localized Ca2+ signals are required to translocate and activate Ca2+-dependent transcription factors (e.g., nuclear factor of activated T-cells, NFAT; histone deacetylase, HDAC) through phosphorylation/dephosphorylation processes.

Keywords: Ca2+, IP3, excitation-contraction coupling, excitation-transcription coupling, cardiomyocyte

Calcium is a pivotal signaling molecule and its intracellular concentration ([Ca2+]i) is precisely regulated in different subcellular domains. The modulation of [Ca2+]i is a crucial factor for a variety of physiological functions of living cells. In cardiac myocytes, including ventricular and atrial cells, Ca2+ release through channels located in the sarcoplasmic reticulum (SR) membrane and termed ryanodine receptors (RyRs), is a key event linking membrane depolarization and mechanical activity during excitation-contraction coupling (ECC) (Bers, 2001). The amount of Ca2+ release with each heart beat and by that the force of contraction is also modulated by hormonal action, e.g., by Endothelin I and Angiotensin II (Proven et al., 2006). These two hormones stimulate plasma membrane receptors (G protein coupled receptors, GPCRs) that couple to phospholipase C (PLC), liberating IP3 from phosphatidylinositol 4,5-bisphosphate (PIP2). IP3 freely diffuses within the cytoplasm to bind to a second type of SR Ca2+ release channels, the inositol 1,4,5-trisphosphate receptor (IP3R) (Roderick and Bootman, 2003; Kockskämper et al., 2008; Berridge, 2009). IP3Rs, albeit at a much smaller density compared to ryanodine receptors (RyR(IP3R ∼100:1), are expressed.
in the SR membrane and nuclear envelope (NE) (Bootman et al., 2009). The activation of IP3 Rs upon binding of IP3 can modulate ECC by sensitizing nearby RyRs leading to positive inotropic but also pro-arrhythmic effects (Petersen et al., 1994; Vogelsand et al., 1994; Zima and Blatter, 2004; Harzheim et al., 2009). Experimental evidence accumulated over the past decade also indicates an important role of IP3 R-mediated Ca2+ release in excitation-transcription coupling (ETC) and pro-hypertrophic signaling (Arantes et al., 2012). The entire PIP2-PLC-IP3 cascade, including GPCRs and IP3 Rs, can be found in the NE (Blaky et al., 2011; Vaniotis et al., 2011; Tadevosyan et al., 2012). The presence of nuclear GPCRs in combination with highly localized nuclear IP3 Rs-mediated Ca2+ release and Ca2+ removal might provide for a putative distinct signaling domain that regulates nuclear Ca2+ dynamics (e.g., for autocrine signaling), whereas the cytosolic Ca2+ is regulated separately via sarcosomal GPCR signaling and IP3 R-mediated SR Ca2+ release in conjunction with Ca2+ release and removal by the set of proteins involved in ECC (e.g., RyR, SERCA, troponin C). Sarcosomal GPCRs allow for paracrine signaling and positive inotropic effects mediated by hormonal stimulation (e.g., with Angiotensin II or Endothelin I), (Kockskämper et al., 2008; Bootman et al., 2009). A comprehensive understanding of the mechanisms regulating nuclear IP3 and Ca2+ signals and the impact of alterations of cytosolic Ca2+ and IP3 signals on nuclear functions requires well-characterized experimental approaches, but also whole-cell system mathematical models. In this review, we discuss quantitative aspects of IP3-dependent Ca2+ homeostasis in adult ventricular and atrial myocytes. In particular, we focus on novel modeling and experimental approaches to support the concept that IP3 R-mediated Ca2+ release and the Ca2+ removal machinery in the SR and NE allow for highly localized and independent cellular signaling.

**EXCITATION-CONTRACTION COUPLING IN VENTRICULAR AND ATRIAL MYOCYTES AND THE ROLE OF IP3**

In cardiomyocytes, ECC describes the process of action potential (AP) triggered Ca2+-induced Ca2+ release (CICR) providing sufficient Ca2+ for the activation of the proteins regulating muscle contraction and to induce active muscle force (Bers, 2001). Membrane depolarization during an AP allows Ca2+ influx through voltage-dependent L-type Ca2+ channels (LTCC) which triggers CICR and thereby amplifies the cytosolic Ca2+ signal to levels required for the activation of the contractile proteins. An important feature of all ventricular myocytes, setting them apart from most atrial cells, is the presence of plasma membrane invaginations throughout the cytosol (transverse or t-tubules), putting LTCC in close vicinity to RyRs (Figure 1). The SR containing RyRs that oppose LTCC is called junctional SR (jSR). The jSR is crucial for the spatiotemporal homogeneity of Ca2+ release leading to largely uniform cytosolic Ca2+ transients ([Ca2+]i) during a ventricular cell twitch (Figure 2), (Frazin-Armstrong et al., 1999; Heinzel et al., 2002; Louch et al., 2004; Crossman et al., 2011; Hake et al., 2012; Signore et al., 2013). Unlike in ventricular cells, the t-tubular system in atrial myocytes is either absent (Figure 1) (Hüser et al., 1996; Kockskämper et al., 2001) or poorly developed (Kirk et al., 2003). However more recent work in sheep and human has provided evidence that atrial cells from larger animals tend to have a higher density of t-tubules (Dibb et al., 2009; Richards et al., 2011), and even in rodent atrial cells an irregular internal transverse-axial tubular system has been identified that affects kinetics of SR Ca2+ release (Kirk et al., 2003). The absence or paucity of t-tubules in atrial cells leads to great differences in the shape and kinetics of local Ca2+ transients and gradients in subcellular regions where Ca2+ is provided by release from jSR and non-junctional SR (njSR) (Figure 2). Subsarcolemmal Ca2+ transients rise faster, have a higher Ca2+ peak and are initiated by Ca2+ currents through LTCCs, followed by RyR-mediated Ca2+ release from the jSR. These local jSR Ca2+ transients resemble Ca2+ release in ventricular cells. Central cytosolic Ca2+ transients, however, have a slower rise time and a lower peak, and result from CICR that propagates in a Ca2+ wave-like fashion from the periphery to the center of the cell. (Blatter et al., 2003; Maxwell and Blatter, 2012). Furthermore, the specific topological organization of the plasma membrane in atrial myocytes leads not only to different spatial [Ca2+]i distribution as compared to the ventricle, it also affects nuclear Ca2+ transients by further delaying their onset due to the wave-like propagation of Ca2+ toward the nucleus (Figure 2). Interestingly, for both atrial and ventricular cells, a role of cytosolic IP3 (IP3) has been reported for the modulation of cytosolic Ca2+ transients in a variety of animal models (Zima and Blatter, 2004; Proven et al., 2006; Domeier et al., 2008; Harzheim et al., 2009; Kim et al., 2010). IP3 R channel activity, with type-2 IP3 Rs as the most prevalent isoform in cardiac myocytes, depends on [IP3]i and [Ca2+]i (Michell et al., 1981; Domeier et al., 2008; Kockskämper et al., 2008). There is evidence that atrial myocytes express functional IP3 Rs at higher densities than ventricular myocytes (Figure 1; in ventricular cell the IP3 Rs are not shown in the junctional space due their relatively low density) (Mackenzie et al., 2004; Zima and Blatter, 2004). As shown in Figure 2, the acute increase in cytosolic IP3, induced by photolytic release of IP3 from a caged IP3 compound, increases cytosolic Ca2+ transient peak amplitudes during field stimulation in atrial cells in contrast to ventricular cells. In ventricular cells only increased expression levels of IP3 Rs, as it occurs in cardiac hypertrophy, could experimentally be tied to enhanced cytosolic SR Ca2+ release (Harzheim et al., 2009). The neurohumoral stimulation with Endothelin I or Angiotensin II, however, has been shown to have similar positive inotropic effects in both ventricular and atrial cells, indicating a role of IP3-mediated Ca2+ release in the enhancement of cytosolic Ca2+ release (Zima and Blatter, 2004).

**EXCITATION-TRANSCRIPTION COUPLING IN VENTRICULAR AND ATRIAL MYOCYTES AND THE ROLE OF IP3**

Nuclear Ca2+ signals however are different with regards to kinetics during action potential induced Ca2+ transients. This can largely be attributed to the fact that the nucleus is surrounded by the nuclear envelope (Kockskämper et al., 2008; Alonso and Garcia-Sancho, 2011), consisting of the outer and inner nuclear membranes and the space between them that is contiguous with the SR (Wu et al., 2006; Shkryl et al., 2012). The nuclear membranes fuse at many locations to form pores (diameter ~100, length ~50 nm) that harbor the nuclear pore complexes (NPCs).
FIGURE 1 | Ca$^{2+}$ and IP$_3$ and their involvement in cardiac excitation-contraction and excitation-transcription coupling in ventricular and atrial myocytes. Schematics depict parts of the sarcolemmal plasma membrane as well sarcoplasmic reticulum and nuclear envelope as a contiguous Ca$^{2+}$ store. Abbreviations: GPCR, G protein-coupled receptor; PIP$_2$, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; LTCC, L-type Ca$^{2+}$ channel; NCX, Na$^+$/Ca$^{2+}$ exchanger; RyR, ryanodine receptor; IP$_3$R, IP$_3$ receptor; SERCA, SR Ca$^{2+}$ ATPase; NCX/GM1, NCX ganglioside complex; CaM, Calmodulin; CaN, Calcineurin; CaMKII, Ca-Calmodulin dependent kinase; NFAT, nuclear factor of activated t-cells; DAG, Diacylglycerol; HDAC, histone deacetylase; NPC, nuclear pore complex; Ca$^{2+}$ released from intra-nuclear pools.

The NPCs are the major gateway for ions (including Ca$^{2+}$) to diffuse along the gradient between the cytosol and nucleoplasm. It has been proposed that NPCs can act as diffusion filter and introduce a kinetic delay in the equilibration of nucleoplasmic Ca$^{2+}$ concentration ([Ca$^{2+}$]$_{\text{nuc}}$) and [Ca$^{2+}$]$_i$ (Bootman et al., 2009). The extent of the kinetic delay might be subject to modulation. Although NPCs do not close, their conductance can change in response to factors such as Ca$^{2+}$ and ATP. The density of NPCs can vary from 1 to 5 NPCs per $\mu$m$^2$, depending on the cell type (Wang and Clapham, 1999). A greater expression of NPCs would allow for a more rapid equilibration of [Ca$^{2+}$]$_i$ and [Ca$^{2+}$]$_{\text{nuc}}$. Recent data from Alonso and García-Sancho (2011) also suggest a role for NE invaginations (nucleoplasmic reticulum) and intra-nuclear Ca$^{2+}$ pools for the regulation of nuclear Ca$^{2+}$ (Figure 1). More evidence that nuclear Ca$^{2+}$ dynamics are not just a function of cytosolic Ca$^{2+}$ transients can be found in structural and functional differences of NE Ca$^{2+}$ handling proteins as compared to the SR. Even though the NE is an extension of the SR (Wang and Clapham, 1999), recent evidence suggests that NE Ca$^{2+}$ handling proteins are not only different from those in the SR, but also that the NE is a major site for Ca$^{2+}$ buffering and regulation (Malviya and Klein, 2006; Bootman et al., 2009). Nonetheless, other putative Ca$^{2+}$ handling and ion transporting proteins have been suggested to be present in the NE, including a splice variant of the type-1 Na$^+$/Ca$^{2+}$ exchanger associated with ganglioside (NCX/GM1 complex, typical for non-excitable cells), RyRs, NAADPR (nicotinic acid adenine dinucleotide phosphate receptor), Na$^+$/K$^+$ ATPase and Na$^+$/H$^+$ exchanger (Gerasimenko et al., 2003; Irvine, 2003; Bkaily et al., 2006; Ledeen and Wu, 2007; Zima et al., 2007; Guatimosim et al., 2008; Wu et al., 2009).

Even more important seems the preferential expression of IP$_3$Rs in the NE (Bare et al., 2005). Using FluO-5N Zima et al. observed a depletion of the nuclear envelope upon experimental stimulation of IP$_3$Rs with IP$_3$ in isolated nuclei (Zima et al., 2007) that was paralleled by an increase of [Ca$^{2+}$]$_{\text{nuc}}$. Wu and colleagues obtained similar results with FluO-5N on IP$_3$ dependent NE Ca$^{2+}$ depletion in permeabilized cells (Wu et al., 2006). The importance of IP$_3$ for the regulation of [Ca$^{2+}$]$_{\text{nuc}}$ is underscored by the results shown in Figure 2: Following cell-wide IP$_3$ uncaging, nuclear Ca$^{2+}$ transients are consistently and preferentially altered in atrial and ventricular cells. However since IP$_3$ is buffered (i.e., by IP$_3$Rs) and degraded over time (Woodcock and Matkovich, 2005), the subcellular localization of IP$_3$Rs and the site of IP$_3$...

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generation (i.e., GPCR) are important to generate highly localized Ca\(^{2+}\) signals to control Ca\(^{2+}\)-dependent transcription (Bers, 2013; Ibarra et al., 2013). The traditional view on the positioning of GPCRs in cardiac myocytes sees their main site of expression in the sarcolemmal and nuclear membrane (Figure 1). Only recently, work from Ibarra et al. (2013) suggested a third type of localization for GPCRs in t-tubules close to the nuclear envelope (Figure 1, ventricular cell). The positioning of IP\(_3\) production and IP\(_3\)Rs is important since differences in the kinetics of local [Ca\(^{2+}\)] can lead to altered activation of transcription factors. A pronounced local elevation of [Ca\(^{2+}\)] for instance, can activate calmodulin dependent–protein kinase II (CaMKII) and promote histone deacetylases (HDAC) phosphorylation (Wu et al., 2006), whereas a sustained smaller [Ca\(^{2+}\)] elevation increases nuclear factor of activated T-cells (NFAT) dephosphorylation via the Ca\(^{2+}\)-sensitive phosphatase calcineurin (CaN). This ultimately leads to the activation of different sets of transcription factors, e.g., myocyte enhancer factor 2 (MEF2) for HDAC and GATA for NFAT (Molkentin et al., 1998). The separate set of Ca\(^{2+}\) release and removal proteins in the NE, with IP\(_3\)Rs as the most prominent example, as well as the specific expression of GPCRs in the sarcolemmal and nuclear membranes might be key to understanding the conundrum of Ca\(^{2+}\) being a modulator of contraction and transcription at the same time (Bootman et al., 2009). Mathematical modeling of nuclear and cytosolic Ca\(^{2+}\) homeostasis, accounting for different expression levels of sarcolemmal, cytosolic and nuclear Ca\(^{2+}\) handling proteins, paralleled by experimental approaches might provide a better understanding of functional differences of nuclear and cytosolic Ca\(^{2+}\).

**EXPERIMENTAL TOOLS FOR MEASURING CYTOSOLIC AND NUCLEAR Ca\(^{2+}\) AND IP\(_3\) SIGNALS**

Confocal laser microscopy, multiphoton imaging and conventional microscopy provide the basis for visualization of whole cell and subcellular ion concentration distributions, and the development of chemical fluorescent Ca\(^{2+}\) indicators

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**FIGURE 2 | Experimental measurement of cytosolic and nuclear Ca\(^{2+}\) and IP\(_3\).** (A) Cardiomyocyte loaded with the caged IP\(_3\) compound cag-IP\(_3\) PM and expressing cytosolic FIRE-1. Whole cell [IP\(_3\)] signal shown as changes in FIRE-1 FRET signal (expressed as F530/F488) after global IP\(_3\) uncaging by exposure to 405 nm laser illumination for 100 ms. (Ba,b) Effects of global IP\(_3\) uncaging (2 ms or 100 ms illumination) in field-stimulated ventricular myocytes on global nuclear and cytosolic Ca\(^{2+}\) transients. (C) The effect of global IP\(_3\) uncaging (2 ms) on global nuclear, subsarcolemmal (j-SR) and central (nj-SR) Ca\(^{2+}\) transients in field stimulated atrial myocyte. (Cb) The effect of global IP\(_3\) uncaging (2 ms) on global nuclear, j-SR and central Ca\(^{2+}\) transients in field stimulated atrial myocyte pre-incubated with the IP\(_3\)R blocker 2-APB. Pacing frequency 0.5 Hz. Black arrowheads indicate application of electrical stimuli.
Ca²⁺ et al. (2006) developed biosensors termed FIRE to dynamically allow for a more complete picture of cell physiology. Only recently Remus effects were confirmed in IP 3R knock-out mice (Li et al., 2005). Ca²⁺ binding affinity is crucial for the selection of the appropriate Ca²⁺ dye for a particular cellular compartment of interest. Low affinity, high Kₐ d dyes (like Fluo-5N) are used for the visualization of changes in SR [Ca²⁺] or nuclear envelope [Ca²⁺], whereas, e.g., Fluo-4 (Kₐ d of 345 nM) is one of the preferred dyes for imaging of changes in cytosolic free [Ca²⁺], which varies roughly between 100 nM and values at times exceeding 1 μM during ECC. Since the nucleoplasm and the cytoplasm are interconnected compartments with similar global [Ca²⁺] characteristics, dyes suitable to show changes in [Ca²⁺], can be used for the detection of changes in [Ca²⁺]nuc as well. Using Ca²⁺ sensitive dyes, Zima and Blatter (2004) were able to visualize cytosolic IP 3R-mediated Ca²⁺ release events (Ca²⁺ puffs) and show a positive inotropic effect of neurohumoral stimulation with Endothelin-1 in cardiac myocytes. As mentioned above, the same group was also able to show changes of local nuclear envelope [Ca²⁺] in isolated nuclei upon stimulation with IP 3, using Fluo-5N (Zima et al., 2007). A variety of pharmacologic interventions can be used to influence the IP 3-dependent signaling cascade. Tools for stimulation of the neurohumoral GPCR pathway in cardiomyocytes include for example Angiotensin II and Endothelin-1. PLC-inhibitors like U73122 and IP 3R blockers like 2-Aminoethoxydiphenyl borate (2-APB) or heparin are widely used IP 3R blockers to study the GPCR/PLC/IP 3 pathway. More recent molecular techniques and targeted to the cytosolic or nuclear compartment. An increase in [Ca²⁺] shows changes of local nuclear envelope [Ca²⁺] in isolated nuclei upon stimulation with IP 3, using Fluo-5N (Zima et al., 2007). Mathematical approaches for simulating cytosolic and nuclear Ca²⁺ and IP 3 signals Computational modeling has proven to be a powerful approach to study cardiac physiology and its implications for disease. With increasing availability of biophysical and physiological data, mathematical models have also become more sophisticated. They provided new insights into how cellular structures, channels and receptor distributions or Ca²⁺/IP 3 signaling regulate cardiac ECC. A number of deterministic models of ventricular and atrial myocyte electrophysiology, intracellular Ca²⁺ handling and bioenergetics have been published. For a more complete review on successes and failures in these modeling pursuits we refer the reader to some excellent recently published articles (Noble, 2011; Jafrı, 2012; Noble et al., 2012; Sobie and Lederer, 2012; Poláková and Sobie, 2013; Wilhelms et al., 2013). Several computational models have been constructed to investigate IP 3 synthesis and the sub-cellular mechanisms regulating IP 3R-mediated Ca²⁺ signaling. The first model of an IP 3 signaling system, built to simulate IP 3 signals in response to stimulation with cardiac hypertrophic neurohumoral agonists like Endothelin-1 and Angiotensin II, was published by Cooling et al. (2007). The key controlling parameters with respect to the resultant cytosolic [IP 3] in atrial cells were identified, including phosphorylation of membrane receptors, ligand strength, binding kinetics to pre-coupled (with GaGDP) receptors and kinetics associated with pre-coupling the receptors. In 1992, De Young and Keizer (1992) constructed the first simplified model of the IP 3 receptor. Subsequent theoretical studies,
The intracellular machinery for Ca$^{2+}$ is characterized by a deterministic model that includes ion channels, NCX, pumps, and IP$_3$ play a key role in the generation of regenerative pacemaker potentials. This model supports the idea that the cyclic changes in cytosolic Ca$^{2+}$ and IP$_3$ play a key role in the generation of regenerative pacemaker potentials. Spatiotemporal continuum models, seeking to investigate the mechanisms of IP$_3$-mediated Ca$^{2+}$ signaling in cells where IP$_3$Rs are known to be the dominant Ca$^{2+}$ release channels, have been published as well. Jafari and Keizer, combining a realistic model of IP$_3$-induced Ca$^{2+}$ oscillations with the diffusion of IP$_3$ and buffered diffusion of Ca$^{2+}$, developed a reaction-diffusion continuum model in Xenopus oocytes (Jafari and Keizer, 1994, 1995). Their results suggest that Ca$^{2+}$ diffusion, which was much slower than that of IP$_3$, because of endogenous Ca$^{2+}$ buffers, had only a small effect on predicted Ca$^{2+}$ transients. These findings imply a possible previous undisclosed role for IP$_3$ in cell signaling. Means et al. (2006) used a reaction-diffusion model to simulate Ca$^{2+}$ and IP$_3$ dynamics in mast cells. The model was built upon a 3D reconstruction of the endoplasmic reticulum (ER) geometry from electron-tomography series. This model simultaneously tracks the changes in cytoplasmic and ER [Ca$^{2+}$], includes luminal and cytoplasmic Ca$^{2+}$ buffers, plasma membrane Ca$^{2+}$ fluxes, SERCA, ER leakage, and type-2 IP$_3$R. A unique feature of the model is the inclusion of the stochastic behavior of Ca$^{2+}$ release. The results showed that IP$_3$Rs in close proximity modulate the activity of their neighbors through local Ca$^{2+}$ feedback effects. Finally, in 1999 an analysis performed by fluorescence measurements of [Ca$^{2+}$]$^\text{intr}$ in ventricular myocytes revealed that [Ca$^{2+}$]$^\text{intr}$ increases concomitantly with [Ca$^{2+}$]$^\text{cyt}$ upon electrical stimulation, but the pattern of [Ca$^{2+}$]$^\text{intr}$ increase was biphasic (rapid and slow) (Genka et al., 1999). Both sets of [Ca$^{2+}$]$^\text{cyt}$ and [Ca$^{2+}$]$^\text{intr}$ data were well fitted by predictions derived from a simplified model of Ca$^{2+}$ diffusion across the NPCs with two different Ca$^{2+}$ diffusion constants. A plausible explanation of this finding is that the change in [Ca$^{2+}$]$^\text{intr}$ is caused by Ca$^{2+}$ diffusion from the cytosol to the nucleus through NPCs, but the permeability of the NPCs shifts from free to moderately restricted during contraction (Genka et al., 1999). The partial restriction of Ca$^{2+}$ diffusion into the nucleus at high [Ca$^{2+}$]$^\text{cyt}$ may support the idea of a defense mechanism protecting the nucleus against Ca$^{2+}$ overload during cell contraction.

Taken together, the aforementioned modeling efforts fill a number of specific gaps of knowledge with respect to cell electrophysiology and cytosolic Ca$^{2+}$ and IP$_3$ signaling. To date, however, no quantitative model coupling the cell electrophysiology with Ca$^{2+}$ and IP$_3$ signaling in the cytosol and nucleus in cardiomyocytes exists. The development of a new system model, coupling ECC and ETC is important because: (a) this tool would provide fundamental new information on the role of IP$_3$Rs on nuclear Ca$^{2+}$ signaling during ECC for arrhythmogenesis, for electrophysiological changes and for nuclear Ca$^{2+}$ signaling in normal and failing cardiac cells; (b) as more experimental details on the complexity of IP$_3$ regulation in myocytes accumulates, the intuitive interpretation of new findings becomes increasingly impractical and sometimes controversial. In pursuing this goal we extended the Shannon-Bers model in rabbit ventricular myocytes (Shannon et al., 2004). New equations, describing nuclear Ca$^{2+}$ dynamics and its dependence on [Ca$^{2+}$], nuclear Ca$^{2+}$ buffering and transport via NPCs and NE (i.e., SR) were incorporated (see Figure 1; Michailova et al. unpublished data). Preliminary results (Figures 3A,B) show that the model predictions are in qualitative agreement with our Ca$^{2+}$ transient measurements at 0.5 Hz electrical stimulation (see Figure 2B) and published experimental data (Ljubojevic et al., 2011) of global cytosolic and nuclear Ca$^{2+}$ transients under control conditions, i.e., in absence of activation of IP$_3$ signaling. The predicted [Ca$^{2+}$]$^\text{cyt}$ and [Ca$^{2+}$]$^\text{intr}$ transients and action potentials and [Ca$^{2+}$]$^\text{SR}$ (not shown) are stable during 10 min stimulation at 0.5, 1, or 2 Hz. The model mimics the frequency-dependent increases in the diastolic [Ca$^{2+}$]$^\text{cyt}$ (Shannon et al., 2004), but no obvious differences in diastolic levels of [Ca$^{2+}$]$^\text{intr}$ vs. [Ca$^{2+}$]$^\text{cyt}$ at any given frequency were predicted. At each frequency the systolic Ca$^{2+}$ peaks were lower in the nuclei and positive force-frequency increases in systolic [Ca$^{2+}$]$^\text{cyt}$ and [Ca$^{2+}$]$^\text{intr}$ were predicted. The kinetic parameters of Ca$^{2+}$ transients (time to peak and time to 50% [Ca$^{2+}$]$_\text{rel}$) were slower in the nucleus compared to the cytosol. The physiological utility of the model was tested further by applying different frequencies to simulate the positive force-frequency relationship (Figure 3C). In agreement with experiments (Ljubojevic et al., 2011), upon increasing the rate from 0.5 to 2 Hz diastolic [Ca$^{2+}$]$^\text{cyt}$ and systolic Ca$^{2+}$ peaks in the nucleus and cytoplasm increased in magnitude and the predicted amplitude of the Ca$^{2+}$ transients were smaller in the nucleus compared to the cytosol.

**CONCLUSIONS AND FUTURE PERSPECTIVES**

In this review we discussed the current state of experimental and modeling approaches to investigate nuclear and cytosolic Ca$^{2+}$ homeostasis, whereby we focused on IP$_3$-dependent Ca$^{2+}$ signaling in adult myocytes. We presented experimental data from ventricular and atrial cells, showing the effects of sudden increases in [IP$_3$] on nuclear and cytosolic Ca$^{2+}$ transients during field stimulation as well as different approaches to study IP$_3$-mediated Ca$^{2+}$ release (i.e., FIRE-1-cyt as a tool to quantify [IP$_3$]), IP$_3$ uncaging to mimic physiological increases in [IP$_3$] and 2-APB to block IP$_3$R mediated Ca$^{2+}$ release). Moreover we compared experimentally the influence of IP$_3$ uncaging on different compartments (nucleoplasm, cytosol) and were able to show that ventricular cells need a stronger IP$_3$ stimulus to elicit a nuclear response, whereas atrial cells display substantial increases in nuclear and cytosolic Ca$^{2+}$ transient amplitude upon a weaker IP$_3$ uncaging stimulus, consistent with their higher total expression of IP$_3$Rs as compared to ventricle. The recent development of FRET-based methods for IP$_3$ and Ca$^{2+}$ imaging in vivo and in situ provides a new opportunity to test whether the predictions of the model hold in vivo and may lead to new hypotheses about the cellular and subcellular distribution of IP$_3$R subtypes and their role in the regulation of Ca$^{2+}$ oscillations.
probes used for the detection of [IP$_3$] as well as approaches to alter nuclear and/or cytosolic [IP$_3$] provide experimental tools for the study of IP$_3$-dependent Ca$^{2+}$ release and its importance in ECC and ETC.

We also presented our recent efforts of a first attempt to develop an electrophysiological and Ca$^{2+}$ signaling model that integrates three different cellular subsystems (cytosol, SR, nucleus) and couples Ca$^{2+}$ dynamics in the cytosol and nucleus. This new tool is under development and will undergo further testing in its prediction of experimental [Ca$^{2+}$]$_{nuc}$ and [Ca$^{2+}$]$_i$ data in rabbit ventricular cells. The proposed model will also be extended to investigate how the complex dynamics of type-2 IP$_3$ receptors (Sneyd and Dufour, 2002; Siekmann et al., 2012), the stochastic behavior of IP$_3$R channel (Fraiman and Dawson, 2004) and/or the stimulation of IP$_3$ signal transduction pathway with neurohumoral agonists (Cooling et al., 2007) regulate ventricular ECC and ETC. Furthermore, the mechanisms underlying IP$_3$-induced positive inotropy in cardiomyocytes continue to be controversial with numerous cellular targets being implicated in the response, including L-type Ca$^{2+}$ channels, K$^+$ channels, and Na$^+$/Ca$^{2+}$ exchange (Lauer et al., 1992; Watanabe and Endoh, 1999; Woo and Lee, 1999; Yang et al., 1999; He et al., 2000; James et al., 2001; Zhang et al., 2001; Puglisi et al., 2011; Signore et al., 2013). The current model can be extended to investigate these effects as well. This model also provides a good quantitative framework to integrate reactions for calmodulin (CaM), calcineurin (CaN), CaMKII, and CaM buffering in the nucleus and can be coupled to the previously described and validated ECC models of CaM-CaMKII-CaN in rabbit ventricular cells (Hund and Rudy, 2004; Grandi et al., 2007; Saucerman and Bers, 2008; Bers and Grandi, 2009; Kraeuter et al., 2010; Soltis and Saucerman, 2010). This will allow testing hypotheses on how the interactions between Ca$^{2+}$, IP$_3$, and CaMKII signaling pathways contribute to heart failure phenotypes. Finally, the tools and insights our group develops will be useful to investigate how perturbations in cytosolic and nuclear Ca$^{2+}$ and IP$_3$ signaling affect ECC and ETC in atrial myocytes (Grandi et al., 2011; Koivumäki et al., 2011).

**AUTHOR AND CONTRIBUTORS**

Designed the work: Anushka P. Michailova and Felix Hohendanner. Performed the experiments: Felix Hohendanner and Lothar A. Blatter. Performed the simulations: Anushka P. Michailova. Analyzed the data: Anushka P. Michailova, Felix...
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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 18 December 2013; accepted: 18 February 2014; published online: 06 March 2014.

Citation: Hohendanner F, McCulloch AD, Blatter LA and Michailova AP (2014) Calcium and IP3 dynamics in cardiac myocytes: experimental and computational perspectives and approaches. Front. Pharmacol. 5:35. doi: 10.3389/fphar.2014.00035

This article was submitted to Pharmacology of Ion Channels and Channelopathies, a section of the journal Frontiers in Pharmacology.

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