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Review

Cardiac inositol 1,4,5-trisphosphate receptors

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ABSTRACT

Calcium is a second messenger that regulates almost all cellular functions. In cardiomyocytes, calcium plays an integral role in many functions including muscle contraction, gene expression, and cell death. Inositol 1,4,5-trisphosphate receptors (IP_3Rs) are a family of calcium channels that are ubiquitously expressed in all tissues. In the heart, IP_3Rs have been associated with regulation of cardiomyocyte function in response to a variety of neurohormonal agonists, including those implicated in cardiac disease. Notably, IP_3R activity is thought to be essential for mediating the hypertrophic response to multiple stimuli including endothelin-1 and angiotensin II. In this review, we will explore the functional implications of IP_3R activity in the heart in health and disease.
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1. Introduction

Cardiac hypertrophy is an adaptive response to a wide variety of cardiovascular diseases such as hypertension, ischemic insults, and cardiomyopathy [1–3]. Ventricular hypertrophy can occur in either the right or left ventricle and usually occurs as a compensatory mechanism to maintain normal contractility. Ventricular hypertrophy is characterized by increased ventricular wall thickness as a means to decrease wall tension and cardiac stress. Sustained pathological hypertrophic remodeling can lead to arrhythmias, heart failure, and sudden death [4].

Hormonal factors such as endothelin-1 (ET-1) are known to contribute to the development of cardiac hypertrophy. ET-1 is a potent vasoconstrictor known to increase in the circulation with age and during cardiac stress [5–8]. In the heart ET-1 regulates cardiac muscle function by modulating contractility, cardiomyocyte size, and cardiac gene expression [9,10]. ET-1 binds and activates the G-protein coupled receptor endothelin receptor type A (ET_A) localized on the cardiomyocyte plasma membrane, leading to activation of phospholipase C (PLC) and production of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) [11–13]. An increase in cytosolic IP_3 leads to calcium release *via* the IP_3R calcium channel. Increases in cytosolic calcium *via* the IP_3R can lead to modulation of cardiomyocyte contraction and activation of signaling pathways that modulate gene expression. Nuclear factor of activated T cells (NFAT) is a transcription factor that is well known to be one of the targets of the ET-1/IP_3R signaling cascade [14–16]. Calcium release through IP_3Rs leads to activation of calcineurin, which is a calcium-activated phosphatase. Dephosphorylation of cytosolic NFAT by calcineurin leads to the translocation of NFAT to the nucleus, where it initiates transcription of different genes that contribute to hypertrophic remodeling. The ET-1 signaling cascade has been extensively studied and it is known to play a crucial role during pathological hypertrophic remodeling of the heart [10,14].

In the heart IP_3Rs are thought to play an important role by modulating calcium signals in response to extracellular stimulation. IP_3R expression levels have been shown to be increased in cardiac hypertrophy, failing myocardium, atrial fibrillation, ischemic dilated cardiomyopathy, and hypertension [17–19]. Cardiomyocyte IP_3R expression is less abundant compared to the main calcium release channel of the heart, the ryanodine receptor (RYR). However, during cardiac hypertrophy IP_3R expression and function is increased, and this is thought to contribute to cardiac remodeling [17,18,20]. To what extent IP_3Rs specifically contributes to the hypertrophic remodeling is not completely understood and somewhat controversial.

2. Regulation of inositol 1,4,5-trisphosphate receptor function

The IP_3R is a ligand-gated calcium channel that is primarily localized to the endoplasmic/sarcoplasmic reticulum (ER/SR). In some cell types, the IP_3R may also be found at the plasma membrane, Golgi apparatus, secretory vesicles, and perinuclear/nuclear membrane [11,18,21]. The IP_3R family is comprised of three isoforms that are encoded by three distinct genes. Each IP_3R isoform is about 300 kDa and they form homo- and hetero-tetramers when co-expressed in different tissues [22–24]. The IP_3R N-terminus contains the ligand (IP_3) binding domain and the suppressor domain. The C-terminal domain has six transmembrane alpha helices that forms an ion conduction pore and a C-terminal tail that is thought to modulate gating by interacting with the ligand

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binding domain from an adjacent subunit [25]. The C-terminal tail is also the site of binding of multiple proteins that modulate channel function, as well as being targeted for post-translational modifications such as phosphorylation [26]. Between the N-terminal ligand binding domain and the C-terminal channel domain the IP_3R has a modulatory domain, which is an additional site of interaction for a variety of proteins and molecules that regulate channel function [27]. The modulatory domain is also a the site for post-translational modifications that are thought to further modulate IP_3-induced calcium release [28–30]. The three IP_3R isoforms share ~60% overall sequence identity, with the N- and C-terminal domains sharing the highest homology between isoforms [31,32]. As expected, the three IP_3R isoforms also share similarities in gating and conductance characteristics consistent with their high sequence homology [33,34]. IP_3R-1 is the main isoform expressed in the central nervous system (and in particular the cerebellum), and is critical for proper central nervous system function as evidenced by the hereditary spinocerebellar ataxias 15/16 and 29 that are caused by deletions/mutations in one allele of the *ITPR1* gene [35,36]. IP_3R-2 is expressed at high levels in the heart, pancreas, liver, and salivary glands. Similar to IP_3R-2, IP_3R-3 is also highly expressed in the pancreas and salivary glands [36]. IP_3R isoform expression is presumed to be regulated in a cell and tissue specific manner [36,37], however the mechanisms regulating differential expression are unclear. Practically speaking, most tissues have detectable levels of all three IP_3R isoforms that can form both homo and heterotetramers [22,24,36,38]. Thus, evaluating or interpreting isoform-specific function *in vivo* is a daunting task.

2.1. Allosteric regulators Of IP_3-induced calcium release

Signal transduction pathways leading to calcium release classically originate at the plasma membrane (PM). Activation of PM receptors can lead to generation of the signaling molecules IP_3 and diacylglycerol through the action of phospholipase C (PLC). IP_3 binding to the IP_3R causes a conformational change that leads to calcium release from intracellular calcium stores. [39]. IP_3-induced calcium release (sometimes abbreviated IICR) can be allosterically regulated by calcium, ATP, and many proteins [40–47]. It has been shown using a wide variety of techniques that the different IP_3R isoforms are differentially regulated by IP_3 [31,37]. It was later confirmed by single channel recording in planar lipid bilayers that IP_3R-2 has the highest affinity for IP_3, followed by IP_3R-1 and IP_3R-3 [33,48]. Much of what we know about IP_3R function, including isoform-specific function, has been elucidated in the DT40 chicken B cell line in which each IP_3R isoform has been knocked out using homologous recombination either singly or in combination [48, 49]. B-cell receptor mediated calcium release in DT40 cells exclusively expressing IP_3R-2 was characterized by calcium oscillations that were more robust and longer-lasting compared to those observed in wild-type cells [48]. On the other hand, IP_3R-1 mediated calcium release was characterized by an initial monophasic calcium response that was followed by irregular calcium oscillations with smaller amplitude compared to IP_3R-2. The IP_3R-3 mediated calcium response was characterized by a single calcium release event, and in contrast to IP_3R-1 and -2, there were no additional calcium oscillations [48]. These studies depict the different functional characteristics of calcium release events mediated by each isoform, at least in the DT40 cell system in response to B cell receptor stimulation. Similar results were obtained using concatenated homo- and heterotetramers [50]. The ligand IP_3 is not the only regulator of IP_3R-mediated calcium release. It has been shown that calcium functions as a co-agonist for IP_3R calcium release at low concentrations while at higher calcium concentrations IP_3R activity is inhibited [51–55]. Therefore, calcium has the ability to bi-phasically regulate IP_3R function. These positive and negative feedback loops contribute to the complex spatio-temporal aspects of calcium release.

The crucial event that activates IP_3R calcium release is the binding of IP_3 to the IP_3R. IP_3R activation by IP_3 is known to be modulated by ATP. Binding of ATP to the IP_3R results in an increase in IP_3R open probability and this modulation is isoform specific [33,40,42,56,57]. Accordingly, each receptor has different affinities for ATP. IP_3R-2 is known to have the highest affinity, approximately 10 fold-higher compared to IP_3R-1. Interestingly, IP_3R-2 is modulated by ATP only at submaximal IP_3 concentrations [42]. IP_3R-3 is known to have a lower affinity compared to the other two isoforms [42]. ATP binds to a glycine rich region (GXGXXG) on the IP_3R that is commonly found in several ATP binding proteins and is known as a Walker motif. IP_3Rs have two of these motifs named ATP-binding motif A and B (ATPA/ATPB) [58]. It is known that the ATPA binding motif is exclusively found on IP_3R-1, while ATPB binding motif is conserved among all three isoforms. Using mutagenesis experiments, it was shown that mutation of the ATP binding motifs on IP_3R-1, ATPA and ATPB, does not abrogate ATP's positive effect on IP_3R-1. Similarly, mutation of IP_3R-3 ATPB binding motif does not affect IP_3R-3 open probability in response to ATP. Thus, available evidence suggests that IP_3R-1 and IP_3R-3 have other still unknown ATP binding sites. In contrast, mutagenesis experiments done on IP_3R-2 show that ATPB is essential for ATP modulation of IP_3R-2 [42,58]. Interestingly, a recent report using recombinant concatemeric IP_3R constructs has shown conclusively that at least two subunits of IP_3R-2 is sufficient to confer ATP sensitivity [59]. In contrast, other functional aspects such as IP_3 sensitivity display an intermediate phenotype. Thus, the difference in IP_3R activation/modulation by IP_3, calcium, and ATP highlights the unique characteristics of each IP_3R isoform that is further enriched by heterotetramer formation. However, the three IP_3R isoforms have been shown to be at least partially functionally redundant *in vivo*.

2.2. Isoform-specific function

It is difficult to assess the importance and role of an individual IP_3R isoform because they are co-expressed in almost all tissues [36,37]. As noted above, *in vitro* studies using DT40 cells revealed differences in IP_3R function between isoforms, and this is likely mediated by distinct regulation by IP_3, calcium, and ATP. DT40 experiments with concatenated receptors also revealed unique properties of heterotetrameric channels [59]. Mutations in IP_3R channels causing human disease have been very instructive for establishing isoform-specific function *in vivo*. Heterozygous mutations of the *ITPR1* gene cause spinocerebellar ataxia (SCA) 15 and 29 [60–64], which are progressive neurodegenerative disorders characterized by cerebellar ataxia and tremors. SCA16 is also caused by mutations in *ITPR1*, and it is now clear that SCA15 and SCA16 are clinically indistinguishable. As such, SCA16 is now considered a "vacant SCA" [65]. SCA15 is an autosomal dominant disorder characterized by a decrease in IP_3R-1 expression that leads to slow degeneration of Purkinje cells of the cerebellum where normally IP_3R-1 is highly expressed [61,66]. Lower amounts of IP_3R-1 cause Purkinje cell degeneration, possibly by the dysregulation of intracellular calcium homeostasis in these cells. The related disorder SCA29 is distinguished clinically by earlier age of onset and cognitive impairment [63,64]. At the molecular level, it is associated with a missense mutation in the regulatory domain. However, the functional consequences at the cellular level of the mutation observed in SCA29 disorder have yet to be determined [64]. Missense, nonsense, and in-frame deletion mutations in *ITPR1* are also the cause of a very rare disease associated with ataxia known as Gillespie Syndrome [67,68]. Interestingly, some Gillespie Syndrome patients have homozygous truncating mutations in the IP_3R protein resulting in what would be predicted to be a complete loss IP_3R-1 calcium release function [68]. Other mutants might function as dominant-negative subunits to inhibit channel function [68]. Thus, the loss of IP_3R-1 function appears to be compatible with life in humans. A homozygous missense mutation in *ITPR2* is a rare cause of isolated anhidrosis with normal sweat glands [69]. The mutation is within the putative selectivity filter of the IP_3R pore, substituting glycine 2498 for serine. This mutation results in normal levels of IP_3R-2 expression in clear cells of the sweat gland, but loss of IP_3R-2 mediated calcium release. Thus the complete loss of IP_3R-2 calcium release function, like

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