Effect of inositol 1, 4, 5-trisphosphate receptor dependent Ca\textsuperscript{2+} release in atrial fibrillation

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To the Editor: Myocardial electrical and structural remodeling are closely related to the pathogenic mechanisms of atrial fibrillation (AF), which mainly result from disordered Ca\textsuperscript{2+} homeostasis in the atrium. Recent evidence showed that altered inositol 1,4,5-trisphosphate receptors (IP\textsubscript{3}R) activity can affect conduction velocity and rhythm in the sinoatrial nodes. The disruption of Ca\textsuperscript{2+} homeostasis mediated by IP\textsubscript{3}Rs is closely associated with the special pathophysiology observed in AF, which involves atrial remodeling, inflammation, and oxidative stress (OS).

The clustered IP\textsubscript{3}Rs demonstrate a higher open probability, compared with that of lone IP\textsubscript{3}Rs, which implies that receptors in the clustered state are more cooperative than isolated ones. Most importantly, the only condition for the IP\textsubscript{3}R\textsubscript{5} activation is under the appropriate concentrations of IP\textsubscript{3} and Ca\textsuperscript{2+}.

When the expression of IP\textsubscript{3}Rs is up-regulated, Ca\textsuperscript{2+} influx in the sarcoplasmic reticulum (SR) can be regulated by the sodium-calcium exchanger (NCX).

Furthermore, Ca\textsuperscript{2+} influx results in Na\textsuperscript{+} influx which triggers the prolongation of the action potential duration and the refractory period, facilitating the maintenance of AF. Importantly, Ca\textsuperscript{2+} and Na\textsuperscript{+} overload provide a pathological basis for early after depolarization and delayed after depolarization, which may also cause AF.

For example, previous study had demonstrated that the incidence of AF was abolished in IP\textsubscript{3}R2-knockout transgenic mice. Atrial structure remodeling is a primary clinical feature of AF, which is termed “the hallmark of the arrhythmogenic substrate,” including fibrosis, enlargement, and fatty infiltration. It is thought to be integral to inhomogeneous conduction contributing to re-entry.

Previous experiments confirmed that IP\textsubscript{3}R\textsubscript{5}s mediate electrical remodeling that can facilitate atrial structural remodeling via enhanced afterload and peripheral resistance.

Post-operative AF can be predicted, based on the detection of circulating C-reactive protein, interleukin (IL)-2, and IL-6 levels in plasma. Atrial inflammation and fibrosis are closely interrelated and associated with similar signaling pathways which have a synergistic effect in triggering heterogeneity in conduction. Transforming growth factor-\beta, as a fibrotic protein, could positively support the release of inflammatory cytokines, pre-disposing individuals to AF.

In addition, IP\textsubscript{3}R-mediated signaling could promote the secretion of inflammatory factors, such as IL-6, IL-8, macrophage inflammatory protein-1\textbeta. Interestingly, 2-aminoethoxydiphenyl borate inhibits the secretion of pro-inflammatory cytokines.

Taken together, these findings suggest that inhibition of IP\textsubscript{3}Rs may abolish the pro-arrhythmic effect of inflammatory cytokines under potential stimulation.

OS occurs due to the imbalance of oxidants and antioxidants, resulting in the opening of mitochondrial permeability transition pores (mPTPs), and subsequently produce reactive oxygen species (ROS). ROS is easier to activate IP\textsubscript{3}R-mediated Ca\textsuperscript{2+} signaling in atria than in ventricles. In most cases, the opening of mPTPs is also controlled by IP\textsubscript{3}R-mediated Ca\textsuperscript{2+} release, which triggers the electrical remodeling in atrium. Thus, OS is detrimental to proper diastolic function and also promotes the development of AF. Pre-treatment with N-acetylcysteine, as IP\textsubscript{3}R\textsubscript{5} inhibitor, can abolish the effects of IP\textsubscript{3}R1-mediated Ca\textsuperscript{2+} overload.

ROS triggers the activation of protein kinase A, C, G (PKA/PKC/PKG), leading to phosphorylation of IP\textsubscript{3}Rs. For example, PKA promotes Ca\textsuperscript{2+} influx into the SR, which enhances its activity by mediating the phosphorylation of IP\textsubscript{3}R1 and IP\textsubscript{3}R2. However, the role of PKA in the regulation of IP\textsubscript{3}R3 remains unclear. Generally, IP\textsubscript{3}R1 must be phosphorylated by PKA at S1589 and S1755 to enhance Ca\textsuperscript{2+} release. For PKC, neferine promoted increased intracellular Ca\textsuperscript{2+} concentration through the PLC-PKC-IP\textsubscript{3}R pathway. However, PKG can selectively phosphorylate IP\textsubscript{3}R3 and prevent Ca\textsuperscript{2+} release in the
initiating phase. Moreover, the PKG activator decreases the amplitude and frequency of Ca^{2+} oscillations in a time-dependent manner. These findings demonstrate that the various protein kinase isoforms may perform different functions in modulating IP_{3}Rs-mediated Ca^{2+} signaling.

It is well known that atrial remodeling, inflammation, and OS are closely associated with the physiological process of cell apoptosis, which finally cause the abnormal of conduction velocity and rhythm in atrial tissues. For instance, Bax and Bak, as members of the anti-apoptotic Bcl-2 family, both decrease Ca^{2+} leakage by regulating the phosphorylation of IP_{3}R1. Additionally Bcl-2 and BAX/BAM can interact with IP_{3}Rs, assembling in a macromolecular complex, which stimulates mitochondrial Ca^{2+} uptake and controls cell apoptosis by modulating Ca^{2+} elevation and ATP metabolism. Therefore, these evidence implies that IP_{3}Rs play a pivotal role in the development and maintenance of AF.

The P1059L mutation in the IP_{3}Rs regulatory domain could increase binding affinity to IP_{3}, which contributes to IP_{3}Rs-mediated Ca^{2+} signals. Interestingly, IP_{3}R1/IP_{3}R2 double-knockout models died in utero at the embryonic stage owing to structural abnormalities in cardiac tissues, such as thin myocardial walls, poor trabeculation, and the absence of the atrioventricular canal. Mutation of lysine 17 within Bcl-2 abolishes the inhibitory effect of Bcl-2 on IP_{3}Rs, thereby preventing excessive Ca^{2+} leakage from apoptosis. Mutations (D1790G) in sodium channels (Nav1.5) can affect the function of IP_{3}R1 via co-localization with calcium/calcmodulin-dependent protein kinase II, which can subsequently cause Na^{+} and Ca^{2+} overload, resulting in arrhythmic disease.

There are many potential mechanisms by which IP_{3}R1 may alter relative protein and trigger the downstream signaling cascade, including ryanodine receptor 2 (RyR2), transient receptor potential canonical 3 (TRPC3), stromal interaction molecule (STIM), and Orai calcium release-activated calcium modulator 1 (ORA1). Functional cross-talk between IP_{3}Rs and RyR2 has been previously observed in human atrial myocytes. Although the expression of IP_{3}Rs is lower than that of RyR2 in cardiomyocytes, IP_{3}Rs

**Figure 1:** Ligand binding to G-protein coupled receptors (GPCRs) and glutamate metabotropic receptor 1 (mGluR1) leads to IP_{3} production though the hydrolysis of PIP_{2}. IP_{3} binds to IP_{3}Rs, which mediates Ca^{2+} leakage from the SR. Phospholipase C (PLC) also generates diacylglycerol (DAG), and subsequently activates PKC/IP_{3}Rs signaling. On the other hand, carbonic anhydrase-related protein (CARP) controls the activity of IP_{3}Rs through binding to modulatory receptors, including IP_{3}Rs, IRBIT, and endoplasmic reticulum protein (ERp44). In addition, CARP can suppress affinity for IP_{3}, and different stimuli can enhance the activity of IP_{3}Rs and mediate Ca^{2+} release (CICR), which triggers OS. Endothelial nitric oxide synthase (eNOS) produces nitric oxide (NO), which stimulates soluble guanylyl cyclase (sGC) to catalyze cyclic guanine monophosphate (cGMP) synthesis from guanosine triphosphate (GTP). This process also leads to PKG activation, which suppresses IP_{3}Rs-mediated Ca^{2+} signaling. Conversely, cAMP is generated by adenylyl cyclase (AC) and promotes IP_{3}R-enhanced Ca^{2+} oscillations. Increased PKB activity can protect cells from a Ca^{2+}-dependent apoptotic stimulus. In the absence or accumulation of Ca^{2+} and IP_{3}, the IP_{3}R is in a closed state and can only be activated at appropriate IP_{3} and Ca^{2+} concentrations. Enhanced IP_{3}R2 expressions can suppress the activity of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a), promoting Ca^{2+} oscillations, ROS accumulation, and cell apoptosis. Inflammation, ROS production, cell apoptosis, and atrial remodeling are related to the underlying pathology of AF. AF: Atrial Fibrillation; IP_{3}R: Inositol 1,4,5-trisphosphate receptors; PKB: Protein Kinase B; PKG: Protein Kinase G; ROS: Reactive oxygen species.
are more abundant in atrial myocytes and RyR2 is more frequently expressed in ventricle myocytes. This might explain why IP3R-mediated Ca2+ influx plays a significant role in manipulating the activity of atrial myocytes. Previous study showed that IP3Rs and RyRs co-localize in the microspace of atrial myocytes, providing a substrate for the modulation of channel gating.[19] However, the mechanisms of channel gating are distinct for IP3Rs and RyRs[20]; therefore, RyR2 and IP3Rs may be associated with independently downstream signaling pathways. For TRPC3, it plays a significant role in mediating cardiac fibrosis, which serves as the etiological basis for AF. In TRPC3 knockout mice, the effect of angiotensin II-induced AF was inhibited. Interestingly, it was confirmed that a complex involving TRPC3, NCX, and IP3R1 contributes to the modulation of Ca2+ homeostasis during the inflammatory response.[6] Moreover, IP3Rs can interact with TRPC3 and together mediate Ca2+ overload which leads to cardiac contractility and arrhythmogenesis. On the other hand, when STIM co-localizes with ORAI1, IP3Rs are activated which leads to Ca2+ leakage from the SR. However, IP3R-mediated Ca2+ release can also activate STIM, leading to the generation of STIM-ORAI1 clusters, which initiates store operated calcium entry (SOCE). Importantly, the activity of SOCE is reversely controlled by STIM/ORAI1 signaling cascades.[21] Therefore, combining with these results, we conclude that IP3Rs interact with STIM and ORAI1, both of which have a synergistic effect in modulating Ca2+ depletion.

Overall, the study summarizes the mechanisms underlying IP3R-mediated Ca2+ leakage and how these correlates with AF pathogenesis, including atrial remodeling, OS, and inflammation [Figure 1]. Both factors can initiate heterogeneity in conduction as a substrate of re-entry. Additionally, IP3Rs trigger a variety of downstream signaling pathways in the modulation of Ca2+ homeostasis. Further research into IP3Rs and related signaling cascades will inform new, targeted strategies for alleviating the morbidity and mortality of AF.

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**Conflicts of interest**

None.

**References**

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