Effect of inositol 1, 4, 5-trisphosphate receptor dependent Ca^{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^{2+} homeostasis in the atrium. Recent evidence showed that altered inositol 1,4,5-trisphosphate receptors (IP_3R) activity can affect conduction velocity and rhythm in the sinoatrial nodes. The disruption of Ca^{2+} homeostasis mediated by IP_3Rs is closely associated with the special pathophysiology observed in AF, which involves atrial remodeling, inflammation, and oxidative stress (OS).

The clustered IP_3Rs demonstrate a higher open probability, compared with that of lone IP_3Rs, which implies that receptors in the clustered state are more cooperative than isolated ones. Most importantly, the only condition for the IP_3Rs activation is under the appropriate concentrations of IP_3 and Ca^{2+}.[1-3] When the expression of IP_3Rs is up-regulated, Ca^{2+} influx in the sarcoplasmic reticulum (SR) can be regulated by the sodium-calcium exchanger (NCX).[4] Furthermore, Ca^{2+} influx results in Na^+ influx which triggers the prolongation of the action potential duration and the refractory period, facilitating the maintenance of AF. Importantly, Ca^{2+} and Na^+ overload provide a pathological basis for early and delayed after depolarization, which may also cause AF. For example, previous study had demonstrated the incidence of AF was abolished in IP_3R2-knockout transgenic mice.[3] 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 affirmed that structural remodeling in the atrium can be easily detected in patients with paroxysmal and permanent AF,[5] and the accumulation of collagen I was inhibited in an IP_3R-deficient model.[6] It has further confirmed that IP_3Rs 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.[7] Atrial inflammation and fibrosis are closely interrelated and associated with similar signaling pathways which have a synergic effect in triggering heterogeneity in conduction. Transforming growth factor-β, as a fibrotic protein, could positively support the release of inflammatory cytokines, pre-disposing individuals to AF. In addition, IP_3R-mediated signaling could promote the secretion of inflammatory factors, such as IL-6, IL-8, macrophage inflammatory protein-1β.[8] Interestingly, 2-aminoethoxydiphenyl borate inhibits the secretion of pro-inflammatory cytokines.[9] Taken together, these findings suggest that inhibition of IP_3Rs 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).[10] ROS is easier to activate IP_3R-mediated Ca^{2+} signaling in atria than in ventricles.[11] In most cases, the opening of mPTPs is also controlled by IP_3R-mediated Ca^{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_3Rs inhibitor, can abolish the effects of IP_3R1-mediated Ca^{2+} overload.[12] ROS triggers the activation of protein kinase A, C, G (PKA/PKC/PKG), leading to phosphorylation of IP_3Rs. For example, PKA promotes Ca^{2+} influx into the SR, which enhances its activity by mediating the phosphorylation of IP_3R1 and IP_3R2. However, the role of PKA in the regulation of IP_3R3 remains unclear. Generally, IP_3R1 must be phosphorylated by PKA at S1589 and S1755 to enhance Ca^{2+} release. For PKC, neferine promoted increased intracellular Ca^{2+} concentration through the PLC-PKC-IP_3R pathway.[13] However, PKG can selectively phosphorylate IP_3R1 and prevent Ca^{2+} release in the

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initiating phase.[14] 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_3Rs-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_3R1. Additionally Bcl-2 and BAX/BAM can interact with IP_3Rs, assembling in a macromolecular complex, which stimulates mitochondrial Ca^{2+} uptake and controls cell apoptosis by modulating Ca^{2+} elevation and ATP metabolism.[15] Therefore, these evidence implies that IP_3Rs play a pivotal role in the development and maintenance of AF.

The P1059L mutation in the IP_3Rs regulatory domain could increase binding affinity to IP_3, which contributes to IP_3Rs-mediated Ca^{2+} signals. Interestingly, IP_3R1/IP_3R2 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.[16] Mutation of lysine 17 within Bcl-2 abolishes the inhibitory effect of Bcl-2 on IP_3Rs, thereby preventing excessive Ca^{2+} leakage from apoptosis.[17] Mutations (D1790G) in sodium channels (Nav1.5) can affect the function of IP_3R1 via co-localization with calcium/calmodulin-dependent protein kinase II, which can subsequently cause Na^+ and Ca^{2+} overload, resulting in arrhythmic disease.[15]

There are many potential mechanisms by which IP_3R1 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 (ORAI1). Functional cross-talk between IP_3Rs and RyRs has been previously observed in human atrial myocytes.[18] Although the expression of IP_3Rs is lower than that of RyRs in cardiomyocytes, IP_3Rs

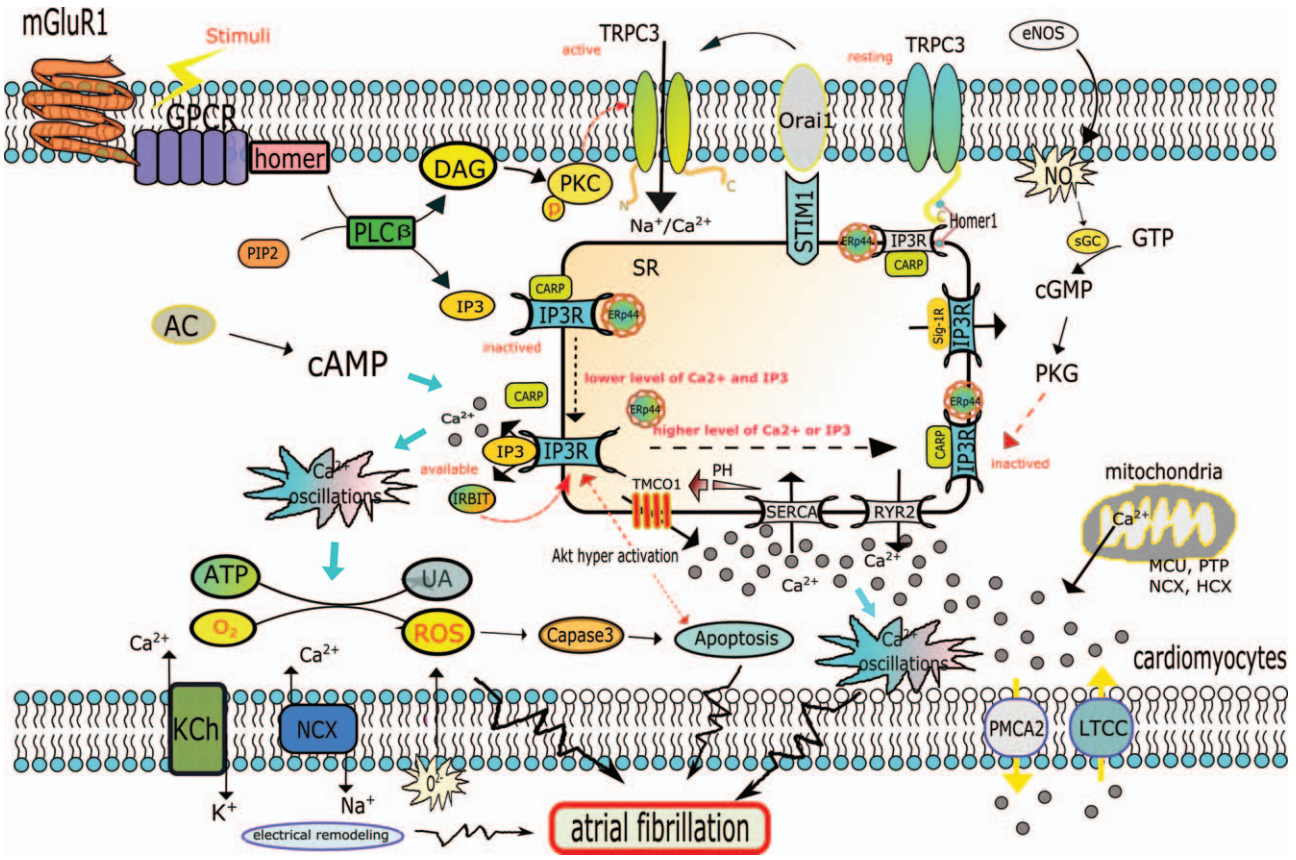

Figure 1: Ligand binding to G-protein coupled receptors (GPCRs) and glutamate metabotropic receptor 1 (mGluR1) leads to IP_3 production though the hydrolysis of PIP2. IP_3 binds to IP_3Rs, which mediates Ca^{2+} leakage from the SR. Phospholipase C (PLC) also generates diacylglycerol (DAG), and subsequently activates PKC/IP_3Rs signaling. On the other hand, carbonic anhydrase-related protein (CARP) controls the activity of IP_3R1 though binding to modulatory receptors, including IP_3Rs, IRBIT, and endoplasmic reticulum protein (ERp44). In addition, CARP can suppress affinity for IP_3, and different stimuli can enhance the activity of IP_3Rs and mediate Ca^{2+}-induced Ca^{2+} release (CICR), which triggers OS. Endothelial nitric oxide synthase (eNOS) produces nitric oxide (NO), which stimulates soluble glanylyl cyclase (sGC) to catalyze cyclic guanine monophosphate (cGMP) synthesis from guanosine triphosphate (GTP). This process also leads to PKG activation, which suppresses IP_3Rs-mediated Ca^{2+} signaling. Conversely, cAMP is generated by adenylyl cyclase (AC) and promotes IP_3-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_3R is in a closed state and can only be activated at appropriate IP_3 and Ca^{2+} concentrations. Enhanced IP_3Rs 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_3R: 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 IP_3R-mediated Ca^{2+} influx plays a significant role in manipulating the automaticity of atrial myocytes. Previous study showed that IP_3Rs 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 IP_3Rs and RyRs[20]; therefore, RyR2 and IP_3Rs 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 IP_3R1 contributes to the modulation of Ca^{2+} homeostasis during the inflammatory response.[6] Moreover, IP_3Rs can interact with TRPC3 and together mediate Ca^{2+} overload which leads to cardiac contractility and arrhythmogenesis. On the other hand, when STIM co-localizes with ORAI1, IP_3Rs are activated which leads to Ca^{2+} leakage from the SR. However, IP_3R-mediated Ca^{2+} 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 IP_3Rs interact with STIM and ORAI1, both of which have a synergistic effect in modulating Ca^{2+} depletion.

Overall, the study summarizes the mechanisms underlying IP_3R-mediated Ca^{2+} 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, IP_3Rs trigger a variety of downstream signaling pathways in the modulation of Ca^{2+} homeostasis. Further research into IP_3Rs 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

1. Piegari E, Villarruel C, Ponce DS. Changes in Ca^{2+} removal can mask the effects of geometry during IP_3R mediated Ca^{2+} signals. Front Physiol 2019;10:1–31. doi: 10.3389/fphys.2019.00964.
2. Navid P, Pichard KH. Structural basis for the regulation of inositol trisphosphate receptors by Ca2+ and IP3. Nat Struct Mol Biol 2018;25:660–668. doi: 10.1038/s41594-018-0089-6.
3. Li X, Zima AV, Sheikh F, Blatter LA, Chen J. Endothelin-1-induced arrhythmogenic Ca2+ signaling is abolished in atrial myocytes of inositol-1,4,5-trisphosphate(IP3)-receptor type 2-deficient mice. Circ Res 2005;96:1274–1281. doi: 10.1161/01.RES.0000172556.05576.4c.
4. Xie A, Zhou A, Liu H, Shi G, Liu M, Boheler KR, *et al*. Mitochondrial Ca2+ flux modulates spontaneous electrical activity in ventricular cardiomyocytes. PLoS One 2018;13:1–17. doi: 10.1371/journal.pone.0200448.
5. Han L, Tang Y, Li S, Wu Y, Chen X, Wu Q, *et al*. Protective mechanism of SIRT1 on Hcy-induced atrial fibrosis mediated by TRPC3. J Cell Mol Med 2020;24:488–510. doi: 10.1111/jcmm.14757.
6. Zhang B, Li M, Yang W, Loor JJ, Wang S, Zhao Y, *et al*. Orai calcium release-activated calcium modulator 1 (ORAI1) plays a role in endoplasmic reticulum stress in bovine mammary epithelial cells challenged with physiological levels of ketone bodies. J Dairy Sci 2020;S0022-0302:30190–30199. doi: 10.3168/jds.2019-17422.
7. Nomani H, Saei S, Johnston TP, Sahebkar A, Mohammadpour AH. The efficacy of anti-inflammatory agents in the prevention of atrial fibrillation recurrences. Curr Med Chem 2020;5:1–23. doi: 10.2174/1389450121666200302095103.
8. Zhu X, Niu Z, Ye Y, Xia L, Chen Q, Feng Y. Endometrium cytokine profiles are altered following ovarian stimulation but almost not in subsequent hormone replacement cycles. Cytokine 2019;114:6–10. doi: 10.1016/j.cyto.2018.11.002.
9. Purvi M, Michael S, Javier AN, David PB. Calcium channel Orai 1 promotes lymphocyte IL-17 expression and progressive kidney injury. J Clin Invest 2019;129:4951–4961. doi: 10.1172/JCI126108.
10. Qin J, Peng ZZ, Li Q, Wen R, Tao LJ. Renal fibrosis and mitochondrial damage. Chin Med J 2018;131:2769–2772. doi: 10.4103/0366-6999.245272.
11. Taylor CW. Regulation of IP3 receptors by cyclic AMP. Cell Calcium 2017;63:48–52. doi: 10.1016/j.ceca.2016.10.005.
12. Atakpa P, van Marrewijk LM, Apta-Smith M, Chakraborty S, Taylor CW. GPN does not release lysosomal Ca2+, but evokes ER Ca2+ release by increasing cytosolic pH independent of cathepsin C. J Cell Sci 2019;1:1–45. doi: 10.1242/jcs.223883.
13. Zhao P, Tian D, Song G, Ming Q, Liu J, Shen J, *et al*. Neferine promotes GLUT4 expression and fusion with the plasma membrane to induce glucose uptake in L6 cells. Front Pharmacol 2019;10:1–22. doi: 10.3389/fphar.2019.00999.
14. Murthy KS, Zhou H. Selective phosphorylation of the IP3 R-I in vivo by cGMP-dependent protein kinase in smooth muscle. Physiol Gastrointest Liver Physiol 2003;284:221–230. doi: 10.1152/ajpgi.00401.2002.
15. Ando H, Kawaai K, Bonneau B, Mikoshiba K. Remodeling of Ca2+ signaling in cancer: regulation of inositol 1,4,5-trisphosphate receptors through oncogenes and tumor suppressors. Adv Biol Regul 2018;68:64–76. doi: 10.1016/j.jbior.2017.12.001.
16. Cui G, Li Y, Ding K, Hao S, Wang J, Zhang Z. Attribution of Bax and mitochondrial permeability transition pore on cantharidin-induced apoptosis of Sf9 cells. Pestic Biochem Physiol 2017;142:91–101. doi: 10.1016/j.pestbp.2017.01.010.
17. Lopez JR, Kolster J, Uryash A, Estève E, Altamirano F, Adams JA. Dysregulation of intracellular Ca2+ in dystrophic cortical and hippocampal neurons. Mol Neurobiol 2018;55:603–618. doi: 10.1007/s12035-016-0311-7.
18. Fuping Z, Wuping L, Linhua W, Chengxi P, Fuqiang Z, Yi Z, *et al*. Tao-Hong-Si-Wu decoction reduces ischemia reperfusion rat myoblast cells calcium overloading and inflammation through the Wnt/IP3R/CaMKII pathway. J Cell Biochem 2019;120:13095–13106. doi: 10.1002/jcb.28582.
19. Joseph SK, Booth DM, Young MP, Hajnóczky G. Redox regulation of ER and mitochondrial Ca2+ signaling in cell survival and death. Cell Calcium 2019;79:89–97. doi: 10.1016/j.ceca.2019.02.006.
20. Yu Y, Zhou CH, Yao YT, Li LH. Downregulation of Na+/Ca2+ exchanger isoform 1 protects isolated hearts by sevoflurane postconditioning but not by delayed remote ischemic preconditioning in rats. Chin Med J 2018;131:756. doi: 10.4103/0366-6999.226907.
21. Taylor CW, Machaca K. IP3 receptors and store-operated Ca2+ entry: a license to fill. Curr Opin Cell Biol 2019;57:1–7. doi: 10.1016/j.ceb.2018.10.001.

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