Basic science for the clinician

The multidimensional role of calcium in atrial fibrillation pathophysiology: mechanistic insights and therapeutic opportunities

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence is increasing with the ageing of the population. Presently available treatment options are far from optimal and new insights into underlying mechanisms are needed to improve therapy. A variety of recent lines of research are converging to reveal important and relatively underappreciated multidimensional roles of cellular Ca2+ content, distribution, and handling in AF pathophysiology. The objective of the present paper is to review the participation of changes in cell Ca2+ and related processes in the mechanisms that lead to AF initiation and maintenance, and to consider the relevance of new knowledge in this area to therapeutic innovation. We first review the involvement of Ca2+-related functions in the principal arrhythmia mechanisms underlying AF: focal ectopic activity due to afterdepolarizations and re-entrant mechanisms. The detailed molecular pathophysiology of focal ectopic and re-entrant activity is then discussed in relationship to the participation of cell Ca2+ changes and Ca2+-sensitive signalling systems. We then go on to consider the participation of Ca2+-related functions in electrical and structural remodelling processes leading to the AF substrate. Finally, we consider the implications for development of new arrhythmia management approaches and future research and development.

Keywords
Atrial fibrillation • Cardiac remodelling • Ion channels • Calcium handling • Antiarrhythmic drug therapy • Structural fibrosis

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its evolving management is the subject of active consideration in Europe and North America.1 Consideration of presently available therapeutic options indicates many important unanswered questions about underlying mechanisms, resolution of which is needed to improve AF management.2 Several recent lines of research have converged to reveal an important and underappreciated role of Ca2+ in AF pathophysiology. The objective of the present paper is to review the participation of changes in cell Ca2+ and related processes in the mechanisms leading to AF initiation and maintenance, and to consider their relevance to the development of new treatment approaches.

Basic mechanistic determinants of atrial fibrillation and role of Ca2+

Figure 1 illustrates the basic electrophysiological mechanisms leading to AF, highlighting the role of Ca2+-related processes. A brief overview will be presented here; for details see relevant review articles.3,4 Atrial fibrillation can be maintained by rapid focal ectopic activity (e.g. from the pulmonary veins) or by re-entry (Figure 1A).3,4 Re-entry requires a vulnerable substrate, as well as a trigger usually provided by spontaneous focal ectopic discharge. The most common causes of focal ectopic activity are afterdepolarizations (Figure 1B): delayed afterdepolarizations (DADs) occurring after full repolarization or early afterdepolarizations (EADs) preceding full repolarization [typically towards the end of the action potential (AP) plateau or early in phase 3

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Delayed afterdepolarizations are caused by inward Na\(^+\)-Ca\(^{2+}\) exchange (NCX) current (\(I_{\text{NCX}}\)), generated by a transient diastolic rise in cytoplasmic Ca\(^{2+}\) concentration: the additional Ca\(^{2+}\) is exchanged for extracellular Na\(^+\) in a 1:3 ionic ratio, generating a net inward movement of positive ions. When DADs reach excitation threshold, spontaneous APs arise. Early afterdepolarizations occur when the AP is excessively prolonged [e.g. by increased inward L-type Ca\(^{2+}\) current (\(I_{\text{CaL}}\)) or by reduced K\(^+\) currents\(^{5}\)] allowing \(I_{\text{CaL}}\) to recover from inactivation and depolarize the cell by allowing Ca\(^{2+}\) to enter. Early afterdepolarizations cause ectopic firing by depolarizing surrounding tissue to excitation threshold. \(I_{\text{NCX}}\) flows during the AP plateau and contributes to EAD-generating AP prolongation.

Re-entry maintenance depends on critical refractoriness and conduction conditions (Figure 1C). The ‘leading circle’ concept

Figure 1 Basic mechanisms underlying atrial fibrillation. (A) Atrial fibrillation can be maintained by rapid focal ectopic activity or re-entry. Re-entry requires a vulnerable substrate and initiating trigger. (B) Cellular mechanisms of focal activity. Ca\(^{2+}\)-related functions are in red. (C) Determinants of atrial fibrillation maintaining re-entrant activity. Left: wavelength = refractory period \(\times\) conduction velocity, determines size of functional re-entry circuits. Right: reduced wavelength allows more simultaneous circuits, making atrial fibrillation termination less likely. Wavelength can be reduced by decreased action potential duration. Ca\(^{2+}\)-related functions that reduce wavelength include decreased \(I_{\text{CaL}}\) and increased Ca\(^{2+}\)-dependent K\(^+\) current (\(I_{\text{KCa}}\)).
posits that functional re-entry establishes itself in the minimum sized circuit for re-entry maintenance, given by the distance (‘wavelength’) the impulse travels in one refractory period (RP): wavelength = RP × conduction velocity. When the number of circuits that the atria can contain is small (Figure 1C, left), re-entry is unstable and AF self-terminates. When the wavelength is reduced (e.g. when RP decreases), the circuits are smaller and more numerous, simultaneous termination of all circuits is unlikely, and AF is sustained (Figure 1C, right). Refractory period depends on action potential duration (APD). Action potential duration is reduced by decreasing inward current (I_{CaL}), or by increasing outward K^+ current. Recent genomic work suggests that a Ca^{2+}-dependent K^+ current plays an important role in AF, likely by controlling APD.

**Detailed role of Ca^{2+}-related processes in atrial fibrillation-related afterdepolarizations**

**Delayed afterdepolarizations**

A detailed analysis of Ca^{2+}-related processes controlling DAD generation is depicted in Figure 2A. Transmembrane Ca^{2+} entry via I_{CaL} triggers systolic Ca^{2+} release from the sarcoplasmic reticulum (SR) into the cytosol through Ca^{2+} release channels known as ‘ryanodine receptors’ (RyRs, RyR2 = cardiac form), a process termed ‘Ca^{2+} induced Ca^{2+} release’. The released Ca^{2+} (reflected by an intracellular Ca^{2+} transient) binds to myofilament proteins and initiates contraction [excitation contraction (EC) coupling]. During diastole, normal resting cytosolic Ca^{2+} levels are restored by Ca^{2+} reuptake into the SR via a Ca^{2+} uptake pump, the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA, SERCA2a = cardiac form), and by Ca^{2+} extrusion into the extracellular space via NCX. Sarco- plasmic reticulum Ca^{2+} ATPase is regulated by the inhibitory protein phospholamban (PLN), with PLN phosphorylation removing SERCA inhibition and increasing SR Ca^{2+} uptake. The key common denominator of DAD generation is abnormal diastolic Ca^{2+} release through RyRs, which causes diastolic Ca^{2+} concentrations to manifest a transient increase that leads to a DAD through NCX (the DAD-generating transmembrane current is often designated I_{ti}, for ‘transient inward current’). The ability of I_{ti} to depolarize cells is tempered by opposing transmembrane outward currents, which can also affect DAD occurrence.

Ryanodine receptors release Ca^{2+} in response to a Ca^{2+} threshold signal. Abnormal diastolic Ca^{2+} release can occur because of excess SR Ca^{2+} load that reaches release threshold, or through enhanced RyR Ca^{2+} sensitivity (Figure 2A). Excess Ca^{2+} load occurs in a variety of clinical conditions and is alsofavoured by increased h_{NaL} (which enhances intracellular Na^{+} concentration, indirectly increasing cell Ca^{2+} via NCX). Ryanodine receptor hyperphosphorylation or RyR mutations associated with catecholaminergic polymorphic ventricular tachycardia enhance RyR Ca^{2+} sensitivity. A detailed representation of the biochemical determinants of RyR function and DAD generation in AF is shown in Figure 3. Not only do DAD promoting conditions lead to AF, but AF itself promotes DAD occurrence. In chronic AF patients, Ca^{2+}/calmodulin-dependent protein kinase type II (CaMKII) is activated by cell Ca^{2+} loading, which enhances Ca^{2+} calmodulin binding, as well as by angiotensin-II-related

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**Figure 2** Cellular mechanisms underlying focal ectopic activity. (A) Delayed afterdepolarizations result from abnormal diastolic Ca^{2+} release from the sarcoplasmic reticulum via RyR2 Ca^{2+} release channels. (B) Early afterdepolarizations result from excessive APD prolongation that allows I_{CaL} to depolarize the cell from the AP plateau.
oxidation.4,6–8 Ca\(^{2+}\)/calmodulin-dependent protein kinase type II activation, along with AF-related activation of protein kinase A (PKA), phosphorylates RyRs.4,6–8 Experimentally, vulnerability to pacing-induced AF due to a gain-of-function RyR2 mutation is reversed by pharmacological or genetic inhibition of CaMKII or its specific RyR2 phosphorylation site, emphasizing the potential importance of CaMKII phosphorylation in AF.9 The Ca\(^{2+}\) sensitivity and closed state stability of RyR2 are also modulated by accessory-binding proteins such as FK506-binding protein (FKBP12.6), 4 and by accessory proteins such as junctophilin, triadin, calsequestrin, and junctin.4,6 Knock-out mice lacking FKBP12.6 exhibit focal atrial ectopy and vulnerability to pacing-induced AF caused by increased SR Ca\(^{2+}\) leak, NCX activation, and DADs.10,11 Atrial fibrillation patients show reduced FKBP12.6 protein expression in the RyR2 macromolecular complex,1 likely contributing to enhanced SR Ca\(^{2+}\) leak. Prevention of CaMKII phosphorylation suppresses SR Ca\(^{2+}\) leak, DADs, and AF in FKBP12.6 knock-out mice, suggesting that CaMKII phosphorylation is central to DAD-associated AF.11 Ca\(^{2+}\)/calmodulin-dependent protein kinase type II activation can also contribute to AF by phosphorylating histone deacetylase (HDAC), derepressing hypertrophic, ion channel, and transporter genes. Ang-II, angiotensin-II; NADPHox, nicotinamide adenine dinucleotide phosphate oxidase.

Figure 3 Molecular mechanisms leading to delayed afterdepolarizations/ectopic activity in atrial fibrillation and novel Ca\(^{2+}\)-related targets and therapeutic opportunities (blue boxes). Delayed afterdepolarizations result from diastolic sarcoplasmic reticulum Ca\(^{2+}\) releases via RyR2 channels. The excess Ca\(^{2+}\) is removed by NCX, creating a depolarizing transient inward current (\(i_{Na}\)). RyR2 dysfunction may result from hyperphosphorylation or sarcoplasmic reticulum Ca\(^{2+}\) overload. Altered RyR2 modulation by accessory proteins like calsequestrin, triadin, junctin, and junctophilin may also cause sarcoplasmic reticulum Ca\(^{2+}\) leak. Phospholamban hyperphosphorylation and reduced sarcoplasm expression dis inhibit SERCA and increase sarcoplasmic reticulum Ca\(^{2+}\) uptake. Protein phosphatase type I inhibition by enhanced sarcoplasmic reticulum compartment inhibitor 1 (I-1) activity contributes to RyR2 and phospholamban hyperphosphorylation. Increased Ca\(^{2+}\) influx enhances Ca\(^{2+}\)/calmodulin binding to the regulatory domain (red) of Ca\(^{2+}\)/calmodulin (CaM)-dependent protein kinase II (CaMKII), disinhibiting the catalytic subunit (grey). After CaMKII activation by Ca\(^{2+}\)/CaM, Ca\(^{2+}\)/calmodulin-dependent protein kinase type II autophosphorylation at Thr287 and oxidation at Met281/282 prevent catalytic domain reassociation/inhibition. Ca\(^{2+}\)/calmodulin-dependent protein kinase type II phosphorylates multiple sarcoplasmic reticulum located proteins and type 4 histone deacetylase (HDAC), increasing HDAC4/14-3-3 binding and type 4 histone deacetylase nuclear export, derepressing hypertrophic, ion channel, and transporter genes. Ang-II, angiotensin-II; NADPHox, nicotinamide adenine dinucleotide phosphate oxidase.
Sarcoplasmic reticulum Ca\(^{2+}\) load is preserved in patients with chronic AF,\(^6,8\) because PLN hyperphosphorylation offsets SR Ca\(^{2+}\) depletion due to enhanced SR Ca\(^{2+}\) leak\(^{12}\) and sarcoplbin, another endogenous SERCA2a inhibitor, is down-regulated.\(^{14}\)

Changes in NCX function directly affect the DAD-generating current \(i_{\text{CaL}}\). Cardiac NCX expression and [Ca\(^{2+}\)]-corrected \(i_{\text{CaL}}\)-amplitude are up-regulated in AF.\(^{6,12}\) Ryanodine receptor 2 changes and NCX overexpression likely underlie spontaneous SR Ca\(^{2+}\) release events in AF patients.\(^{6,8,15}\)

**Early afterdepolarizations**

Early afterdepolarizations result from factors that increase APD (Figure 1B). Several molecular changes can contribute to atrial EADs by prolonging APD (Figure 2B). Late Na\(^{+}\) current \(i_{\text{NKa}}\) is increased in AF patients,\(^6\) possibly because of enhanced CaMKII activity,\(^9\) increasing plateau inward current and prolonging APD. Atrial fibrillation related to EAD mechanisms may also result from gain-of-function mutations in \(i_{\text{CaL}}\) or \(i_{\text{K_{Na}}}\) that cause Long-QT Syndrome.\(^{7,18}\) Loss-of-function K\(^{+}\) channel mutations, either in K\(^{+}\) channels causing Long-QT Syndrome or in atrial selective channels like \(i_{\text{K}_{\text{Ca}}\text{V1}}\), have been associated with AF, likely by causing EAD-related ectopic activity.\(^{19,20}\) \(i_{\text{CaL}}\) recovery from inactivation, enhanced NCX and CaMKII phosphorylation of Ca\(^{2+}\) channels all contribute to EAD occurrence.\(^{21}\)

**Detailed role of Ca\(^{2+}\)-related processes in re-entrant mechanisms underlying atrial fibrillation**

**Control of repolarization**

At the simplest level, Ca\(^{2+}\)-related mechanisms affect the likelihood of re-entry via their role in determining APD. Decreased \(i_{\text{CaL}}\) reduces atrial cardiomyocyte APD, strongly favouring re-entry. The clearest example is in AF-induced electrical remodelling,\(^3,4\) discussed extensively below. Loss-of-function mutations reducing \(i_{\text{CaL}}\) decrease ventricular APD, causing Short-QT Syndrome and ventricular arrhythmias, but also predispose to AF by decreasing atrial APD.\(^{22}\) Recent work has highlighted the importance of small conductance Ca\(^{2+}\)-dependent K\(^{+}\) channels (SK channels) in governing AF risk in man.\(^4\) The mechanism(s) underlying this association is unclear, and could include either gain or loss of atrial cardiomyocyte K\(^{+}\) channel function, as well as SK channels in non-cardiomyocyte cells.\(^{23}\) Gain of SK channel function should accelerate atrial repolarization and promote re-entrant AF. There is evidence that SK channels may be important in the arrhythmogenic properties of pulmonary veins, and that SK channel up-regulation might contribute to AF promotion by electrical remodelling.\(^{24}\)

**Ca\(^{2+}\) and atrial electrical remodelling**

Atrial arrhythmogenic remodelling refers to a change in atrial structure or function that promotes atrial arrhythmogenesis. Atrial fibrillation, or any other form of rapid atrial tachyarrhythmia, induces changes in atrial electrical properties that promote AF.\(^3,4\) Figure 4 illustrates the mechanisms underlying this process, often termed atrial tachycardia remodelling (ATR). A principal component is reduced atrial APD, which decreases the atrial RP and consequently the wavelength, thereby favouring AF maintenance.\(^8\) Atrial tachycardia remodelling reduces APD both by decreasing inward \(i_{\text{CaL}}\)\(^{25}\) and by increasing outward K\(^{+}\) currents, particularly the inward rectifier currents \(i_{\text{K}_{\text{1}}+}\) and constitutively active acetylcholine-regulated K\(^{+}\) current \(i_{\text{K}_{\text{ACHc}}}\).\(^3,4\) In addition to decreasing APD, increased inward rectifier K\(^{+}\) current hyperpolarizes atrial cardiomyocytes, thereby increasing Na\(^{+}\) current availability, excitability, and re-entrant rotor stability during AF.\(^{26}\)

Cell Ca\(^{2+}\) couples rapid atrial rates to the molecular changes occurring under atrial fibrillation, or any other form of rapid atrial tachyarrhythmia, but also predispose to AF by decreasing atrial APD.\(^{27}\) Cell Ca\(^{2+}\) loading increases cell Ca\(^{2+}\) content, engaging a series of molecular changes that diminish Ca\(^{2+}\) entry and attenuate Ca\(^{2+}\) loading.\(^{27}\) An important rapid reaction system is Ca\(^{2+}\) binding to the \(i_{\text{CaL}}\) channel, which causes partial Ca\(^{2+}\)-dependent \(i_{\text{CaL}}\) inactivation, reducing current and APD within minutes.\(^{28}\) Increased cell Ca\(^{2+}\) enhances Ca\(^{2+}\)/calmodulin-binding and activates Ca\(^{2+}\)-dependent cell signalling. Calcineurin is a Ca\(^{2+}\)/calmodulin-sensitive phosphatase, which dephosphorylates nuclear factor of activated T-cells (NFAT), allowing NFAT to translocate to the nucleus.\(^{29}\) Nuclear factor of activated T-cells translocation regulates mRNA transcription, leading to decreased mRNA expression of the L-type Ca\(^{2+}\) channel pore-forming \(\alpha\)-subunit, decreased \(i_{\text{CaL}}\) and reduced APD/Ca\(^{2+}\) loading.\(^{27}\)

Cell Ca\(^{2+}\) loading also contributes to K\(^{+}\) current up-regulation. In addition to its regulation of \(i_{\text{CaL}}\), NFAT also binds to regulatory DNA regions upstream to the sites encoding the pre-microRNA (miR) corresponding to miR26, inhibiting its transcription.\(^{29}\) Consequently, miR26 expression is down-regulated in AF.\(^{29}\) MicroRNAs reduce translation and can destabilize mRNA of target genes, playing important roles in cardiac remodelling.\(^{29}\) Kir2.1 is the major molecular contributor to \(i_{\text{K}_{\text{1}}+}\). Kir2.1 mRNA has binding sites for miR26, so that miR26 down-regulation removes miR26 suppression of Kir2.1 protein production, increases \(i_{\text{K}_{\text{1}}+}\) and promotes AF.\(^{29}\)

Another component of ATR-induced AF promotion is the enhancement of \(i_{\text{KACHc}}\).\(^{30,32}\) \(i_{\text{KACHc}}\) is carried by \(i_{\text{K}_{\text{ACHc}}}\) channels, but is active in the absence of acetylcholine.\(^{30}\) It is up-regulated in clinical AF,\(^3,1\) and contributes to ATR-induced APD reduction and AF promotion.\(^{32}\) Recent work indicates that ATR enhances \(i_{\text{KACHc}}\) via altered protein kinase C (PKC) function.\(^{31,33,34}\) \(i_{\text{KACHc}}\) is differentially regulated by PKC isosforms, with conventional Ca\(^{2+}\)-dependent isosforms (\(\alpha, \beta\)) inhibiting and novel Ca\(^{2+}\)-independent isosforms (\(\delta, e\)) enhancing channel opening. An important signal in \(i_{\text{KACHc}}\) enhancement is Ca\(^{2+}\)-dependent activation of the proteolytic enzyme calpain, which breaks down PKC\(\alpha\) and removes its inhibition of \(i_{\text{KACHc}}\) opening.\(^{34}\)

**Ca\(^{2+}\) and atrial structural remodelling**

Structural remodelling is an important contributor to AF pathophysiology.\(^4,3,5,36\) Structural remodelling occurs both at cellular (Figure 5A) and tissue (Figure 5B) levels. Atrial cardiomyocytes exposed to long-term rapid activation show loss of myofibrils,
glycogen accumulation, mitochondrial changes, chromatin and connexin redistribution.35,37 These changes are reminiscent of hibernating myocardium; while they may be autoprotective, they might also contribute to AF promotion and atrial contractile impairment.37

Ca$^{2+}$-dependent calpain activation plays a central role in myofilament degeneration.38 Angiotensin-II is an important contributor to AF-related remodelling; angiotensin-II-induced changes in gene expression may be signalled via nuclear-localized angiotensin receptors coupled to gene expression via nuclear Ca$^{2+}$ mobilization through inositol trisphosphate receptor Ca$^{2+}$ channels.39

Atrial fibroblasts are activated in AF, proliferate, and differentiate into collagen-secreting myofibroblasts.40 Myofibroblast accumulation can contribute to AF both via direct electrical interactions with cardiomyocytes and by enhanced secretion of extracellular matrix (ECM) proteins such as collagen,40 inducing atrial fibrosis that interferes with muscle bundle continuity and impairs conduction, thereby promoting re-entry.41 Fibrosis contributes to the AF substrate in many patients, particularly under conditions of atrial dilation/stretch like heart failure.42 Recent work suggests that Ca$^{2+}$ entry through non-selective transient receptor potential (TRP) channels TRPM7 and/or TRPC3 is central to AF-related fibroblast activation.43,44 Fibroblasts from AF patients show up-regulated TRPM7 currents and enhanced Ca$^{2+}$ entry, along with enhanced myofibroblast differentiation, all of which are suppressed by TRPM7 knockdown.43 Fibroblast TRPC3 expression is increased in AF, mediates angiotensin-induced Ca$^{2+}$ entry, and contributes to fibroblast proliferation/differentiation.44 Interestingly, TRPC3 expression appears to be controlled by miR26,44 creating a link between signalling for electrical and structural remodelling. Rapidly firing atrial cardiomyocytes discharge substances that promote fibroblast differentiation, potentially contributing to the atrial fibrosis and therapeutic resistance that develop with longstanding AF.4 Altered myofibroblast K$^{+}$ channel expression can favour AF promotion by influencing electrical interactions with cardiomyocytes and/or affecting Ca$^{2+}$-regulated ECM protein production.45
Novel therapeutic approaches targeting Ca\(^{2+}\)-related components of atrial fibrillation pathophysiology

**Strategies for prevention of Ca\(^{2+}\)-related focal ectopy**

The molecular changes in Ca\(^{2+}\)-related signalling and related proteins offer a variety of opportunities to correct defective Ca\(^{2+}\) handling (Figure 3). Several lead compounds targeting RyR2 diastolic Ca\(^{2+}\) leak have been identified. The local anaesthetic tetracaine stabilizes RyR2 channels in their closed states, whereas the class IC antiarrhythmic drugs flecainide and propafenone have been reported to reduce RyR2 open probability by decreasing mean open time, an observation that has recently been disputed. Newer RyR2 inhibitors based on the structure of the β-blocker carvedilol prevent DAD-related arrhythmias by reducing mean RyR2 open time, thereby suppressing spontaneous SR Ca\(^{2+}\) releases. Stabilization of the RyR2 channel complex is another potential approach. The 1,4-benzothiazepine derivative JTV519 (K201) attenuates AF inducibility in dogs, RyR2-induced SR Ca\(^{2+}\) leak and arrhythmogenic activity in pulmonary vein cardiomyocytes, likely by increasing the affinity of FKBP12.6 for RyR2, and is a potential lead compound. Blockade of forward (Ca\(^{2+}\) extrusion)-mode NCX with benzyloxyphenyl analogues such as KB-R7943, SEA0400, SN-6, and YM-244769 should suppress DADs/triggered activity, but with a risk of promoting Ca\(^{2+}\) overload.

An alternative approach to target SR Ca\(^{2+}\) leak is to reduce CaMKII activity. Proof of principle has been obtained in mouse AF models and small molecule inhibitors are under development. Local targeting of kinase or phosphatase function (e.g. targeting of inhibitor-1 of PP1) is another possible strategy: inhibition of I-1-mediated PP1-suppression normalizes RyR2 phosphorylation and prevents inducible ventricular arrhythmias. Finally, antioxidant molecules could prevent CaMKII activation by angiotensin-II/NADPH oxidase-related oxidant stress.

**Figure 5** Structural remodelling at cellular (A) and tissue (B) levels. (A) Rapidly firing atrial cardiomyocytes show dedifferentiation, glycogen accumulation, myofibrillar degeneration, chromatin changes, and mitochondrial changes. Calpain activation by Ca\(^{2+}\) loading causes myofibril protein breakdown. Angiotensin II acts on nuclear angiotensin type 1 receptors to induce nuclear Ca\(^{2+}\) mobilization via inositol trisphosphate receptor channels (IP3Rs), altering gene expression. Atrial fibrillation and atrial fibrillation-inducing pathology cause fibroblast proliferation and differentiation into myofibroblasts, in part due to diffusible products from rapidly firing cardiomyocytes. Signalling molecules such as angiotensin II contribute to fibroblast proliferation via Ca\(^{2+}\) entry through transient receptor potential channels. (B) Schematic cardiac muscle bundle, with cardiomyocytes in pink, collagen in yellow and myofibroblasts in orange. Direction of longitudinal conduction is shown by black vertical arrows. At the tissue level, myofibroblasts secrete collagen, causing fibrosis that interferes with atrial tissue conduction. Myofibroblast–cardiomyocyte interaction can directly slow conduction and elicit focal activity.
Targeting atrial fibrillation due to re-entry

Although it is theoretically possible to prolong atrial RP by enhancing $I_{\text{Cal}}$, there would be a risk of inducing ventricular EADs and acquired long-QT syndrome. $I_{\text{KCa}}$ is a potentially interesting target: small molecule inhibitors have shown AF suppressing properties in small animal models. Alternatively, nuclear Ca2+-dependent arrhythmogenic remodelling is another possible strategy. Molecular motifs for $I_{\text{K}}$ block have been explored and provide opportunities for drug development. $I_{\text{K(Ca)}}$ blockers are also under development and have efficacy for AF in ATR atria.

Another approach is to target Ca2+-dependent processes leading to arrhythmogenic remodelling, so-called ‘upstream therapy’. $I_{\text{Cal}}$ down-regulation can be prevented by inhibiting steps in the signal transduction pathway, but the agents required are too toxic for in vivo use. Diminishing Ca2+-dependent calpain activation.

Conclusions

A great deal has been learned about the role of Ca2+ in AF. Ca2+-related processes are central to basic atrial arrhythmia mechanisms and to a variety of extremely important AF-promoting remodelling paradigms. Appreciating these processes has given us important new insights into the pathophysiology underlying AF, and will hopefully in due course provide a variety of safe and effective new treatment options.

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