Atrial fibrillation (AF) is common and is associated with significant cardiovascular morbidity and mortality, with stroke being the most critical complication. Present drugs used for the therapy of AF (antiarhythmic and anticoagulants) have major limitations, including incomplete efficacy, risks of life-threatening proarrhythmic events and bleeding complications. Non-pharmacological ablation procedures are efficient and apparently safe, but the very large size of the patient population allows ablation treatment of only a small number of patients. These limitations largely result from limited knowledge about the underlying mechanisms of AF and there is a hope that a better understanding of the molecular basis of AF may lead to the discovery of safer and more effective therapeutic targets. This article reviews the current knowledge about AF-related ion-channel remodelling and discusses how these alterations might affect the efficacy of antiarrhythmic drugs.

Abstract

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Keywords

Atrial fibrillation, remodelling, ion channels, mechanisms

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Prolonged episodes of AF alter atrial properties ("atrial remodelling") promoting AF maintenance (see Figure 1). Changes in atrial structure or function that constitute atrial remodelling are key elements in the AF-substrate. Remodelling increases the likelihood of ectopic firing or re-entry, thereby promoting AF initiation and/or maintenance. Ion-channel remodelling shortens the effective refractory period (ERP) by reducing APD. Spatially heterogeneous ERP abbreviation promotes the conduction block and wave break underlying fibrillatory conduction and APD shortening contributes to AF-related atrial contractile dysfunction. Atrial fibrillation promotes atrial fibrillation because the rate of new-circuit formation exceeds the rate of circuit extinction, continuously maintaining AF episodes.

The likelihood of re-entry is determined by the tissue properties of conduction and refractoriness (for detailed discussion see), with slow conduction and short refractoriness making persistence of re-entry more likely.

Another mechanism potentially involved in AF is ectopic activity, which is governed by factors controlling the occurrence of afterdepolarisations, primarily Ca2+-handling abnormalities that can cause delayed afterdepolarisations (see Figure 1). Ectopic activity can also result from excessive action potential duration (APD) prolongation, which produces early afterdepolarisations. It remains to be shown whether early afterdepolarisations contribute to AF pathophysiology.

Fundamental Atrial Fibrillation Mechanisms

The mechanisms underlying AF induction and maintenance are incompletely understood, but it is generally accepted that re-entry is the major mechanism of AF maintenance. Re-entry induction requires an appropriate vulnerable substrate, as well as a trigger that initiates re-entry within the substrate (see Figure 1).

Single-circuit re-entry can maintain AF by functioning as a rapid driver that induces fibrillatory conduction. Multiple-circuit re-entry involves coexisting functional re-entry-circuits that maintain fibrillatory activity because the rate of new-circuit formation exceeds the rate of circuit extinction, continuously maintaining AF episodes.

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The rapid atrial rate increases potentially cytotoxic Ca$^{2+}$ loading. Cells rapidly protect themselves by reducing L-type Ca$^{2+}$ current (I_{Ca,L}) at the expense of decreased action potential duration (APD). Decreased APD ameliorates refractoriness and decreases the wavelength (Wl) allowing for smaller re-entry circuits, a larger number of which can now be accommodated. In addition to decreased I_{Ca,L}, persistent AF increases the inward rectifier K$^+$ currents I_{K1} and constitutive I_{K,ACh} and decreases connexin-40 (Cx40) and sodium current I_{Na} by changing either gene expression and/or protein regulation (proteolysis and altered phosphorylation or nitrosylation). This contributes to the APD shortening and conduction slowing that promote AF. AF is associated with abnormal function of ryanodine receptor channels (RyRs) producing increased diastolic sarcoplasmic reticulum Ca$^{2+}$ leak. This is amplified by the generation of an enhanced inward Na$^+$-Ca$^{2+}$-exchange current (INa), promoting delayed afterdepolarisations (DADs) and ectopic activity, further favouring AF maintenance. Ectopic activity from pulmonary veins may trigger AF. Sinus-sinus rhythm. See text for further details.

Figure 1: Mechanisms Underlying Promotion of Atrial Fibrillation by Atrial Ion Channel Remodelling

Studies in animal models and in patients with chronic AF have shown that the following are major contributors to APD shortening:2–3,17

- decreased L-type Ca$^{2+}$ current (I_{Ca,L});
- increased inward rectifier K$^+$ current (I_{K1});
- constitutively-active acetylcholine-independent K$^+$ current (I_{K,ACh,C} enhanced repolarisation power).

Initially the resulting shortening of APD helps to compensate for initial Ca$^{2+}$ overload (see Figure 2), but this occurs at the expense of decreased ERP, which favours re-entry.2,3 The shorter refractoriness together with an unchanged sodium current (I_{Na}) may promote the induction of high-frequency sources (rotors). These undergo complex, spatially distributed conduction block patterns with wavefront fractionation manifesting as ‘fibrillatory conduction’ that maintains AF.24

Long-term AF causes profound alterations in atrial structure (cardiomyocyte hypertrophy, glycogen accumulation and interstitial fibrosis).25,26 These lead to inhomogeneous conduction slowing that promotes the development of anatomically-fixed re-entry circuits. Atrial remodelling is clinically important as it explains the transition of paroxysmal to persistent AF,27 the larger resistance of persistent AF to treatment35–36 and higher AF recurrence rate in the first days after cardioversion.28

Ion-channel Remodelling in Atrial Fibrillation

As introduced above, the AF-related shortening of the APD can be attributed to decreased inward currents, enhanced outward K$^+$ currents or a combination of both. Depolarising inward I_{Na} and I_{Ca,L} currents are balanced by a diversity of repolarising K$^+$ outward currents (see Figure 2). The main human atrial repolarising K$^+$ currents include:

- the transient outward current, I_{To};
- the ultra-rapidly activating delayed rectifier current, I_{Kur};
- the rapid (I_{K1}) and the slow (I_{Ks}) activating delayed rectifier currents; and
- the three inward rectifier currents, I_{K1}, I_{K,ACh} and ATP-sensitive I_{K,ATP}.

There is also evidence for the existence and role of Ca$^{2+}$-dependent small conductance potassium channels (SK channels) and transient receptor potential channels in shaping the human atrial AP (see below). Whether and how they contribute to remodelling in AF is currently unknown.

The molecular mechanisms leading to the repolarisation changes in AF are only partially understood. Increased atrial rate causes cellular Ca$^{2+}$ loading,29 which alters cellular Ca$^{2+}$-signalling leading to functional I_{Ca,L} inactivation, which attenuates initial Ca$^{2+}$ overload.30 Persistent AF produces sustained Ca$^{2+}$ loading that is offset by the decreased function of I_{Ca,L} and by increased Ca$^{2+}$ extrusion via the Na$^+$-Ca$^{2+}$-exchanger. These compensatory changes limit cytotoxic Ca$^{2+}$ influx but cause further ERP abbreviation, favouring multiple circuit re-entry (see Figure 1).31–33 The increase in intracellular Ca$^{2+}$ is likely a primary signal for altered gene expression34 and regulation of ion channels.

Molecular Changes of I_{Ca,L} Alterations

Sodium current (I_{Na}) density is reduced in a canine model of atrial tachycardia remodelling (ATR), with corresponding decreases in channel mRNA and protein expression.17 Such changes could contribute to the atrial conduction slowing seen in AF. Despite this theory, Gaborit et al. did not find evidence of atrial I_{Na} changes at the genomic level in AF patients.18 Data obtained in atrial myocytes from AF patients showed either unchanged or only slightly reduced I_{Na} amplitude.

Molecular Determinants of I_{Ca,L} Alterations

Reduced I_{Ca,L} density is a consistent finding in animal models of ATR and patients with AF.17–18 In control cardiomyocytes, inhibition of I_{Ca,L}
with calcium-channel inhibitors mimics the APD abbreviation in ATR and AF. Reduced ICa,L was therefore initially considered as the only determinant of refractoriness shortening in ATR and AF. Subsequent studies, however, indicated important contributions of increased Ikr along with constitutively active IKr,α,β. The molecular basis of decreased ICa,L in ATR and AF is complex and likely depends partly on underlying heart disease.

Transcriptional down-regulation of the Cav1.2 subunit, due to initial Ca2+ overload, is one potential mechanism of reduced ICa,L density. Direct measurements demonstrated that rapid pacing quickly increases cardiomyocyte intracelluar Ca2+. In addition to this, recent in vitro studies of tachypaced dog atrial cardiomyocytes directly confirmed that Ca2+ influx via ICa,L itself and the related Ca2+ overload are major determinants of the transcriptional down-regulation of ICa,L.

Here, Ca2+-calmodulin/calcineurin-related mechanisms were implicated in modification of transcription. Some subsequent studies at the mRNA and protein level confirmed the reductions in Cav1.2 subunit abundance, whereas other reports found no change in protein amount or dithryoprotein receptor density in AF, suggesting the existence of alternative mechanisms.

There is evidence for increased Ca2+-channel dephosphorylation by increased activity of type-1 (PP1) and type-2A (PP2A) serine/threonine protein phosphatases in AF that is expected to reduce the open probability, potentially explaining the decreased ICa,L amplitude. Defective regulation of ICa,L by inhibitory src-type tyrosine kinases may also participate in ICa,L dysregulation. S-nitrosylation of the Cav1.2 subunit is increased in AF and exogenously applied glutathione partially restores the AF-related ICa,L reduction. Thus, oxidative stress could play an important role in ICa,L changes.

Finally, some, but not all, investigations detected decreased expression of accessory β1, β2a, α2δ subunits. These may also contribute to the reduction of ICa,L.

**Mechanisms of Altered Voltage-gated K+ currents**

Iop amplitude is consistently reduced in animals with ATR and in AF patients. The functional consequences of impaired Iop are unclear, but reduced Iop might facilitate wave propagation by indirectly increasing the upstroke velocity of the atrial AP.

In ATR and AF, reductions in Iop are paralleled by decreases in both mRNA and protein expression of the pore-forming Kv4.3 subunit, with calpain-mediated proteolysis likely contributing to decreased Kv4.3 protein levels. CaMKII activity is enhanced in ATR and in AF patients. CaMKII accelerates Iop inactivation, but the higher PP1 and PP2A activity in AF could offset the enhanced CaMKII effect. Ca2+-dependent protein phosphatases, such as calcineurin, may suppress Kv4.3 gene transcription via a nuclear factor of activated T-lymphocyte-dependent mechanism because calcineurin activity is increased in AF.

Results about the function of the ultra-rapid delayed-rectifier Ikr are discrepant, showing either unchanged or reduced Ikr function in AF. The contribution of Ikr to atrial repolarisation depends on AP morphology and is increased with short-duration triangular APs, as occur in AF. For this reason, Ikr may contribute more strongly to atrial repolarisation in AF cardiomyocytes.
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Recent work suggests that the reduced receptor-mediated $I_{K,ACH}$ activation is related to a loss of channel control by cardiac receptors. This leads to increased agonist-independent constitutive $I_{K,ACH}$, both in dogs with ATR$^{29,30}$ and in patients with chronic, but not paroxysmal, AF.$^{24,27}$ Blockade of constitutive $I_{K,ACH}$ suppresses ADP abbreviation and AF promotion in ATR preparations,$^{27}$ indicating that constitutive $I_{K,ACH}$ contributes to ATR-induced atrial arrhythmogenesis.

Agonist-independent constitutive $I_{K,ACH}$ results from the enhanced open probability due to the increased frequency of channel openings.$^{25,26}$ mRNA and protein expression of Kir3.1 and Kir3.4 subunits are unchanged in experimental ATR.$^{28}$ In AF patients, however, the mRNA and protein levels of both subunits are decreased.$^{29,30,32,34}$

In atrial myocardium, $I_{K,ACH}$ is localised in a macromolecular complex including catalytic subunits of PKA, PKC, CaMkII, PP1 and PP2A.$^{23}$ Altered composition of this complex in AF may lead to abnormal phosphorylation-dependent $I_{K,ACH}$ regulation. Blockade of PKC reduces, whereas inhibition of protein phosphatases increases, constitutive $I_{K,ACH}$ activity$^{29}$ and the abundance of PKCε protein is enhanced in AF.$^{26}$ This clearly suggests that PKC-hyperphosphorylation of $I_{K,ACH}$ may underlie the AF-related development of agonist-independent constitutive $I_{K,ACH}$ activity.$^{25}$

ATP-sensitive inward rectifier $K^+$ currents ($I_{K,ATP}$) are important contributors to ischemia-induced changes in cardiac electrophysiology and atrial ischaemia is likely to occur, particularly in persistent AF. $I_{K,ATP}$ amplitude is higher in myocytes from AF patients under ischaemic conditions,$^{22}$ whereas $I_{K,ATP}$ activation in response to agonists like rilmakalim is strongly limited.$^{32}$

Data about expression of the pore-forming Kir6.2 subunit are inconsistent.$^{24,25,27}$ They suggest a complex and perhaps clinical condition-dependent regulation of $I_{K,ATP}$ in AF.

Remodelling of Ion Channels Involved in Atrial Conduction

Ventricular expression and function of the major cardiac connexin, connexin-43, is reduced by structural remodelling (gap junctional remodelling) and these changes correlate with pro-arrhythmic conduction slowing.$^{25}$ Phosphorylation of connexins by different kinases determines connexin trafficking, gap junction assembly and channel-gating properties. Dephosphorylation and redistribution to lateral cell borders are prominent and important determinants of cardiac conduction disturbances.$^{24,25}$

Relatively little is known about gap junctional remodelling in the atria, with discrepant results in the literature showing unchanged, increased and decreased connexin isofrom expression.$^{24,25,27}$ It is possible that the specific connexin alteration depends on the time course, underlying cardiac pathology and animal model used.$^{26}$ Spatially heterogeneous connexin-40 remodelling is observed in the well-controlled goat AF-remodelling system.$^{28}$ This is consistent with the extensive clinical evidence pointing to disturbances in connexin-40 as a basis for genetic AF predisposition.$^{24,26}$

Remodelling of Other Plasmalemmal Ion Channels

Canonical transient receptor potential channels contribute to abnormal Ca$^{2+}$ signalling in hypertrophy (for recent review see$^{29}$) and are potentially involved in arrhythmias.$^{30}$ Type-1 and type-3 transient receptor-potential channels are expressed in the human atrium of patients with diseased hearts. Transient receptor potential channel 3 protein expression is higher in animals with sustained AF and in AF patients.$^{31}$ This suggests transient receptor potential channel 3 proteins as potential novel contributors to AF-related ion-channel remodelling.

In a recent genome-wide association study, a single nucleotide polymorphism that lies within the gene encoding a specific small conductance K$^+$ channel (SK3) was associated with lone AF.$^{32}$ Human atria express three different SK channel subunits (SK1–3).$^{33}$ Overexpression of SK2 channels in mice shortens atrial AP,$^{34}$ whereas SK2 knock-out prolongs APD and induces early afterdepolarisations.$^{35}$ SK channels appear to contribute to pacing-induced shortening of APD in rabbit pulmonary veins.$^{36}$ Although SK2 and SK3 channels are potential novel contributors to AF-related ion-channel remodelling, their precise roles in atrial remodelling require further extensive examination and validation.

Remodelling of Ion Channels and Transporters that Contribute to Atrial Ectopic Activity

Multiple studies have shown that abnormal SR Ca$^{2+}$ handling may play a central role in the initiation and/or maintenance of AF in humans.$^{37,38}$ Defective Ca$^{2+}$-based handling was shown to predispose to spontaneous sarcoplasmatic reticulum (SR) Ca$^{2+}$ release events in atrial myocytes from patients with chronic AF.$^{39,40}$ SR Ca$^{2+}$ load is not increased in chronic AF patients,$^{41,42,43}$ suggesting that these spontaneous SR Ca$^{2+}$ releases most likely occurred because of alterations in ryanodine receptor channels (RyR2) and the resulting increase in diastolic SR Ca$^{2+}$ leak. Phosphorylation of RyR2 at Ser2808 (or Ser2809, depending on the species$^{24}$) by PKA and at Ser2814 (or Ser2815 depending on species)$^{45}$ by CaMkII is higher in dogs with pacing-induced chronic AF and patients with chronic AF. These posttranslational alterations increase the sensitivity of RyR2 to cytosolic Ca$^{2+}$ and enhance the open probability,$^{46}$ providing a possible molecular mechanism for aberrant RyR2 function in AF.

It is very likely that enhanced RyR2 activity plays a role in AF pathogenesis, as mice with a gain-of-function mutation in RyR2 or knock-out of the RyR2-inhibitory FKBP12.6 subunit exhibit an increased susceptibility to pacing-induced AF.$^{47,48}$ Using these mice models it was demonstrated that increased SR Ca$^{2+}$ leak in atrial myocytes can promote triggered activity and atrial arrhythmias.

Altered RyR2 function in chronic AF is accompanied by an increase in Na–Ca$^{2+}$-exchanger expression and function.$^{49,50}$ This suggests that diastolic SR Ca$^{2+}$ leak can be amplified by the Na–Ca$^{2+}$-exchanger, thereby triggering delayed afterdepolarisations and subsequent ectopic focal discharges or facilitating micro-re-entry circuits promoting AF maintenance. In addition to this, IP$_3$ receptor (IP$_3$R)-mediated SR Ca$^{2+}$ release may also facilitate SR Ca$^{2+}$ leak via RyR5s, which promotes atrial arrhythmogenesis,$^{51}$ and protein expression of IP$_3$R2 is increased in a model of ATR.$^{52}$ IP$_3$R2-coupled amplification of atrial SR Ca$^{2+}$ release events and related arrhythmogenesis may thus be an important contributor to AF-related ectopic activity.

Therapeutic Consequences of Ion-channel Remodelling

The changes in ion-channel function caused by AF alter the response to antiarrhythmic drugs, principally making AF more drug-resistant.$^{53}$
A poorer response of more prolonged AF has been shown for both Na+- and K+-channel blockers. 12,13 Early detection and termination of AF increases the clinical effectiveness of pharmacological cardioversion. 5 A strategy of early cardioversion:

- reduces atrial remodelling; 114
- prevents atrial dysfunction; 15
- reduces atrial size; and 15
- may prolong sinus-rhythm maintenance in the post-cardioversion period. 12,13,15

Despite this, there is little evidence from clinical trials for the therapeutic value of an early cardioversion strategy. 12,13

Ion-channel remodelling provides a potential antiarrhythmic drug target. Both the T-type Ca2+-channel blocker mibefradil 118 and amiodarone 10 suppress APD as an index of ion-channel remodelling. I K,ACh 10,11 contributes to amiodarone’s superior efficacy in AF. 12 Bepridil, a L- and T-type Ca2+-channel blocker, also suppresses ion-channel remodelling indices, an action that may explain bepridil’s unusual ability to convert long-standing AF. 13 Inward rectifier K+ currents, such as constitutive I K,ACh, provide a promising approach because they do not affect ventricular repolarisation. 33 However, due to the remodelling effectiveness of I K,ACh, drugs targeting atrial-selective channels such as I K,ACh and constitutive I K,ACh may prove to be more effective and accelerating AF-sustaining rotors than reduction of I Ca,L. 12 Selective inhibition of I K,ACh with the I K,ACh-blocker teretiapin prolongs APD in ATR-remodelled canine preparations and suppresses tachyarrhythmias. 5 AVE0118 and flecainide both inhibit constitutive I K,ACh in chronic AF patients, 14 an effect that might contribute to their effectiveness in terminating AF. However, I K,ACh pore-channel blockers effectively terminate AF, they could also have off-target effects in the brain, gastrointestinal and urinary tracts. Despite this, targeting the pathology-specific molecular mechanisms of constitutive I K,ACh may be an effective and safe anti-AF approach that does not interfere with physiological cholinergic agonist-stimulated I K,ACh function.

There is emerging evidence of increased diastolic SR Ca2+-leak through RyR2 channels and enhanced Na+-Ca2+-exchanger function. This may cause delayed after depolarisations and triggered activity contributing to AF maintenance. Such effects suggest that the development of new drugs specifically targeting arrhythmogenic diastolic SR Ca2+-leak might offer unique therapeutic opportunities to reduce atrial arrhythmogenesis by normalising SR Ca2+ handling (for detailed discussions see 11,119,120). Inflammation and tissue oxidation are believed to be important mediators in ion-channel remodelling 5 Drugs with anti-inflammatory and antioxidant properties, such as glucocorticoids 121 and statins, 122 suppress atrial electrical remodelling, and have shown some clinical value in preventing AF recurrence. 123,124 Suppression of ion-channel remodelling may thus prove to be a useful principle, as either a primary or adjunct property of new antiarrhythmic drugs.

Conclusions

The past decade has provided important insights into key determinants of ion-channel remodelling in both experimental paradigms and clinical AF. Despite major advances, understanding about the underlying molecular mechanisms leading to and perpetuating ion-channel remodelling during AF is very limited. Better knowledge and deeper insights into the molecular mechanisms underlying AF may help to identify new and atrial-selective drug targets for the improved treatment of AF.
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