Novel Pharmacological Strategies for Antiarrhythmic Therapy in Atrial Fibrillation

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Main Elements of the Pathomechanism of Atrial Remodelling

Atrial fibrillation (AF), the most common cardiac disorder, rarely induces sudden/arrhythmogenic cardiac death; however, considering its clinical course it cannot be considered as a benign heart disease at all. The coordinated electromechanical heart function in sinus rhythm (SR) is changed to uncoordinated atrial activity in AF characterised by extremely high frequencies (400-800/min), rendering the atria unable to perform regular muscle contractions. The decreased ventricular filling due to the lack of a proper atrial systole and the irregular ventricular depolarisations/contractions caused by erratic impulse conduction from the atria are responsible for a 10-25% reduction in cardiac output.

The functional andumoror structural changes that create a substrate for repetitive renewal of the arrhythmia, thus contributing to atrial remodelling in AF include: a) functional and morphological injuries of atrial myocytes (sarcolemmal ion channels, signalling and functioning proteins), cell-surface adhesion molecules and coupling structures (gap-junctions), the extracellular matrix, and the endocardial endothelium; b) dysfunction of neurohumoral systems, e.g., the autonomic nervous system and renin-angiotensin-aldosterone system (RAAS).

The most significant electrophysiological changes occurring during AF are depicted in Figure 1. In most cases arrhythmia is induced by an atrial extrasystole (ES). The reentry activity responsible for AF maintaining is based on anatomical and/or functional conductivity block(s), the coexistence of at least or more than five to six small or large activating wavefronts (multiple wavelets) rotating in the inexcitable/refractory heart regions.[1,2]

Figure 1B is a schematic illustration of pathophysiological changes that probably play a role in the induction of AF. Three arrhythmogenic factors may cause venoatrial extrasystoles and, consequently AF via: 1) increased automaticity; 2) reentry; 3) triggered activity as delayed afterdepolarisations (DADs) or early afterdepolarisation (EADs). AF is initiated when ectopic activity triggers reentry in a vulnerable substrate. Instable membrane potentials either at the AP plateau or resting level (EADs, DADs) can serve as a trigger for ectopic activity. Currently it is largely known that in the pulmonary sleeve veins and in some vestigial anatomical structures exist cell types that qualify for spontaneous automaticity/pacemaker activity. These can form ectopic foci, which could initiate single- or multiple-circuits reentry.[2]

Electrical, Structural and Contractile Remodelling

The shape and duration of action potential (APD) are determined by the equilibrium between the relative intensity of the inward ionic currents (especially by the inward L-type Ca^{2+} current) and of the outward repolarising K^+ currents. At the very core of electrical remodelling lies the shortening of the atrial effective refractory period (AERP) and APD, respectively within minutes after the initiation of AF, rendering a triangular shape to the AP (Figure 2). The AERP shortening is due mainly to the loss of function (downregulation) of the I_{CaL} together with the increase (upregulation) of several K^+ current densities and/or membrane permeability.[3,4] According to our current knowledge, the three most likely components responsible for atrial electrical remodelling, APD shortening and triangularisation, are as follows: 1) downregulation of $I_{Ca,L}$; 2) upregulation of I_{K1}; 3) activation of the constitutive (ligand independent) $I_{K,ACh}$. A more detailed description about the effect of electrical remodelling on all known important cardiac transmembrane currents is provided in several comprehensive papers.[1,5]

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The frequency of atrial activation becomes extremely high in AF (400-600/min) therefore in spite of the shorter APD plateaus, the amount of calcium (Ca^{2+}) entering the myocytes significantly increases leading to impaired intracellular Ca^{2+} homeostasis (Ca^{2+}-mishandling).[6] The elevated Ca^{2+}-influx increases the activation of ryanodine receptors (Ca^{2+}-release [RyR2]-channel) leading to a higher number of arrhythmogenic Ca^{2+} sparks.[7] The cells respond to Ca^{2+}-overload by reducing the expression of Ca^{2+}-channels (downregulation), that within a relatively short time significantly shortens APD.[8] Impaired Ca^{2+} homeostasis also manifests in deterioration of contractile (contractile remodelling) and diastolic function of the atria with subsequent wall stiffness and increased stretch that with the time will cause left atrial dilation. Dilation and geometric deformation of the atria are the most important pathomorphological factors determining the propensity for AF recurrence (structural remodelling), the key factor responsible for the deteriorating nature of AF (paroxysmal → persistent → permanent).

Two types of electrical and contractile remodelling exist: a rapid one, which occurs within minutes to hours, and a chronic one that develops in days or weeks.[9] However, both electrical and contractile remodelling is fully reversible after conversion to AF. Conversely, the development of structural remodelling is a slower process, but may cause irreversible morphological alterations within three to four months. Microfibrosis and left atrial dilation are the changes that will hamper the pharmacological conversion of AF and/or the maintenance of SR.[10,11]

Prevention and Therapy of Atrial Remodelling

Therapeutic Principles and Treatment Options in AF

Restoration of normal SR (rhythm control) represents the optimal therapeutic goal in AF. Whilst rhythm control usually requires a combination of pharmacological and non-pharmacological treatments, rate control involves other mechanisms including prolongation of atrioventricular nodal refractoriness or slowing of AV node conduction. The latter can be achieved by several classes of antiarrhythmic drugs, including β-blockers, calcium channel blockers or amiodarone.[12]

Suppression of hyper-excitability of pulmonary veins or atrial tissue can terminate AF by eliminating ectopic triggers and hence support rhythm control. Classical antiarrhythmic drugs used to reach this goal include Na^+ channel blockers or multiple ion channel blockers such as amiodarone.[13] According to the leading wavelet concept,[1,14] short refractoriness and slow conduction will increase the likelihood of reentry. Theoretically, the reentry circuits can be interrupted when conduction is enhanced and refractoriness prolonged so that the reentrant wavefront will reach tissue that is still in refractory state. Available antiarrhythmic drugs can prolong refractoriness but will slow instead of enhancing conduction via blocking the Na^+ channels.

Novel Pharmacological Drugs/Compounds for the Treatment of AF

Currently available antiarrhythmic drugs for the treatment of AF are far from being ideal, and impose serious concerns regarding efficacy and safety. An ideal drug against AF should suppress atrial triggers and disrupt atrial reentry circuits by prolonging atrial refractoriness and slowing intra-atrial conduction. Its atrial selectivity should minimise the ventricular proarrhythmic effects and be safe in patients with concomitant cardiovascular disease, in particular coronary artery disease and heart failure. This is called the atrial selective drug concept. Novel compounds can block specific or multiple ion channels, preferably in an atrial-selective manner, and they can be directed at non-ion channel targets including upstream inflammatory or infiltrative processes or they may influence gap-junctions (Figure 3 and Table 1).

Specific and Multiple Ion Channel Blockers

Numerous class III or repolarisation-delaying compounds have been partly developed and then abandoned, largely because of the risk of *torsades de pointes* brought about by their detrimental effects on ventricular repolarisation. These drugs are especially specific or multiple blockers of the main repolarising potassium currents especially I_{Kr}, I_{Ks}, I_to, I_{K1}, I_{KATP} etc. The main ion channel blocker drugs or investigational compounds used/designed for treating AF are as follows: azimilide (I_{Kr} and I_{Ks} blocker),[15,16,17] HMR-1556 (I_{Ks} blocker),[18,19] AZD-7009 (I_{Kr} and I_{Na}blocker),[20,21,22] dronedarone (amiodarone derivate multichannel blocker)[23,24,25,26,27] and tedisamil (multichannel blocker).[28,29,30,31]

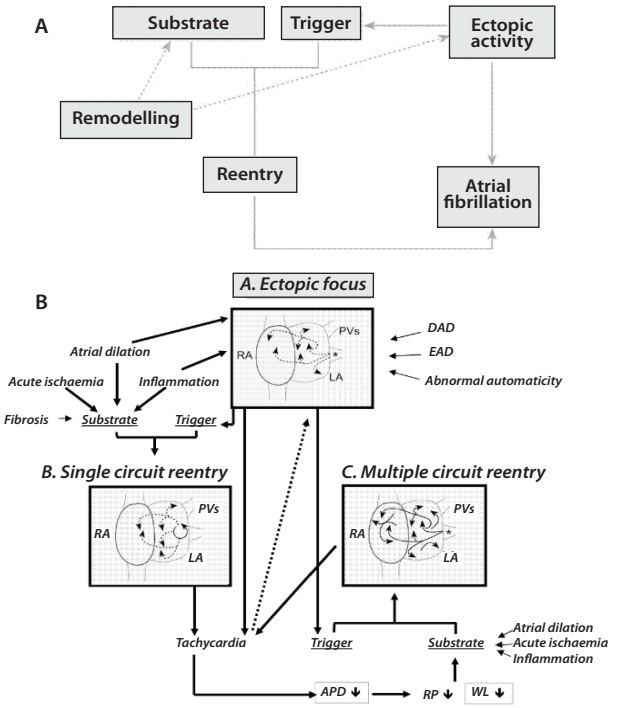

Figure 1. Panel A. Main factors that induce and maintain AF.
Panel B. AF is initiated by an extrasystole started from a pacemaker region (usual left upper pulmonary vein), created by atrial tachycardia remodelling (APD shortening). The electrical perpetuator may be a single/mother wave and/or multiple wave/circuit reentry. Atrial ischaemia and inflammation are known reentry facilitators. The key factors of structural/morphological remodelling are atrial myocardial (micro)fibrosis and left atrial dilation. (AF = atrial fibrillation; RA = right atrium; LA = left atrium; EAD = early afterdepolarisation; DAD = delayed afterdepolarisation; PVs = pulmonary veins; APD = action potential duration; RP = refractory period; WL = wavelength). Modified from Ref [1] with permission. control of AF.

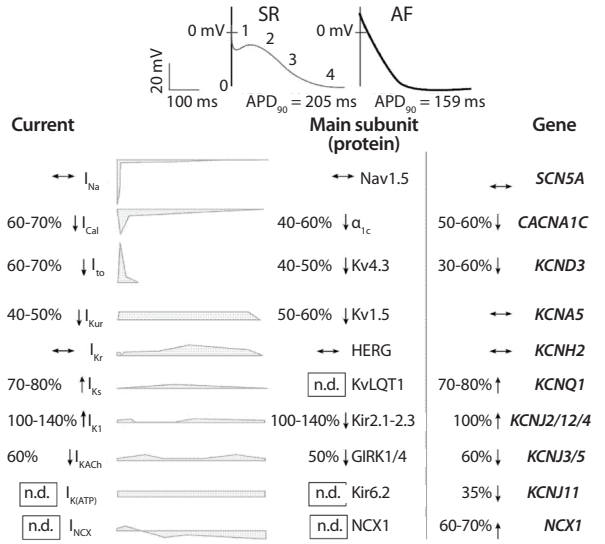

Figure 2. Transmembrane ionic currents determining atrial action potential in sinus rhythm (SR) and in atrial fibrillation (ion channel remodelling). Left column depicts ionic current densities, while middle and right columns show the changes in the expression of the main current subunit putative proteins and genes, respectively. Pictograms present current amplitude and time course more or less considering real size ratios. n.d.: no data available.

Atrial Selective Ion Channel Blockers

A novel strategy for development of agents against AF in order to avoid ventricular proarrhythmic effects is the development of so-called atrial selective drugs. A great deal of effort has been invested into the development of atrial specific ion channel blockers to avoid ventricular arrhythmogenic effects of currently available drugs. Atrial specific targets for AF treatment include the ultra-rapid delayed rectified potassium current (I_{Kur}), the acetylcholine-regulated inward rectifying potassium current ($I_{K,ACh}$), the constitutively active $I_{K,ACh}$ (CA_$I_{K,ACh}$ *i.e.*, which does not require acetylcholine or muscarinic receptors for activation), and connexin 40 (Cx40). The channels responsible for I_{Kur} and $I_{K,ACh}$ are exclusively or nearly exclusively present in atria and largely absent in the ventricles. In addition to atrial specific ion channels, there are ion channels that are present in both chambers of the heart but the inhibition of these channels (especially fast I_{Na}) can produce predominant electrophysiological changes in atria vs. ventricles according to Antzelevitch theory.[32]

The main atrial selective ion channel blocker drugs or investigational compounds used or designed for treating AF are as follows: AVE0118 (I_{Kur} and I_{to} blocker),[33,34,35] XEN-D0101 and DPO-1(selective I_{Kur} blockers)[36,37,38] and vernakalant (I_{Kur}, I_{Na} and I_{Nal} blocker),[39,40] ranolazine (I_{Na} and I_{NaL} blocker),[41,42,43] NIP-142 and NIP-151 ($I_{K,ACh}$ and CA $I_{K,ACh}$ blockers).[44,45]

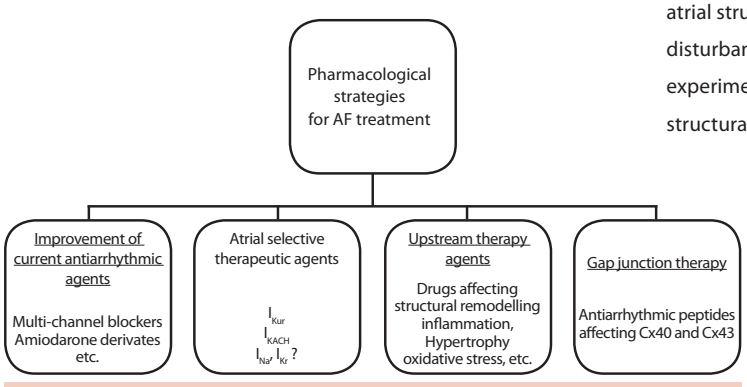

Figure 3. Current prominent investigational strategies for rhythm control of AF.

Na^+/Ca^{2+} Exchanger Current Modulators

The Na^+/Ca^{2+} exchanger current (NCX) exchanges one intracellular Ca^{2+} ion for three extracellular sodium ions. During rapid atrial rates caused by AF or pacing, a larger increase in intracellular sodium relative to calcium may cause the exchanger to work in the reverse mode, bringing calcium into the cell, thus contributing to the shortening of the action potential. Since DADs elicited by NCX1 activity[61] can trigger AF, block of the exchanger has been proposed as a useful antiarrhythmic mechanism. However, available blockers of NCX current, KB-R7943[47] and SEA 0400[48,49] possess only poor highly selective inhibiting properties to test whether NCX blockade indeed would be ideal drugs for combating AF.

Gap Junction Modulators

Electrophysiological and structural remodelling of the fibrillating atria involves changes in junctions at the atrial intercalated discs. Two major isoforms of connexins, Cx40 and Cx43, are specific for the heart.[50] There are several studies that investigated the function of gap junctions during early acute ischaemia, which provided evidence suggesting that closing of gap junctions causes conduction velocity slowing.[51] Several peptides such as rotigaptide (GAP-486, ZP123)[52,53] and GAP 134[54] have been developed, which by preventing gap junction closing, offer a protective effect against AF.

Non Ion-channel Blockers - Upstream Therapy of AF

In addition to further developing ion channel based AF therapy, there is rapid development of non ion-channel approaches, aimed at reducing or reversing structural remodelling, inflammation, and oxidative stress injury associated with AF. These are generally referred to as upstream therapies.[55,56]

It has been known for some time that inflammation and oxidative injury promote structural remodelling, including interstitial fibrosis, fibroblast proliferation, accumulation and/or redistribution of collagen, chamber dilation, and hypertrophy. Proarrhythmic actions of atrial structural remodelling are generally related to conduction disturbances, which promote reentrant arrhythmias. A number of experimental and clinical studies have shown that drugs affecting structural remodelling, inflammation, and/or oxidative stress such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins may reduce the occurrence of AF,[56,57,58] although some studies question the efficacy of such therapies in AF.[13,59,60,61] Successful development of upstream therapy depends on our ability to identify factors and signalling pathways involved in the generation of atrial structural remodelling, inflammation, and oxidative stress.[62,63,64,65] Moreover, the relative role of

	Drugs or investigational compounds	Effects	Preclinical studies	Clinical studies	References
Improvement of current antiarrhythmic agents	Azimilide (FDA approval)	Primarily I_{Kr} and I_{Ks} blocker but additionally blocks I_{CaL} and I_{Na} (multi-channel blocker)	Several in *vitro* and in *vivo* animal models	ALIVE, A-STAR, A-COMET I and II Studies	[15, 16,17]
	HMR-1556	Highly selective I_{Ks} blocker	Several in *vitro* and in *vivo* animal models	not	[18,19]
	AZD7009	Primarily I_{Kr} and I_{Na} blocker, but additionally blocks I_{to}, I_{Kur} and I_{Ks} (multi-channel blocker)	Several in *vitro* and in *vivo* animal models	small centre clinical trial	[20,21,22]
	Dronedarone (FDA approval)	Amiodarone like multichannel blocker (I_{Na}, I_{Ca}, I_{Kr} blocker)	Several in *vitro* and in *vivo* animal models	ADONIS, ATHENA, EURIDIS etc	[23,24,25,26,27]
	Tedisamil	Multichannel blocker (I_{Na}, I_{to}, I_{Kr}, I_{Ks}, I_{KATP}, blocker)	Several in *vitro* and in *vivo* animal models	small centre clinical trial	[28,29, 30,31]
Atrial selective therapeutic agents	AVE0118	Primarily I_{Kur}, I_{to} and $I_{K,ACh}$ blocker	Several in *vitro* and in *vivo* animal models	not	[33,34,35]
	XEN-D0101	Highly selective I_{Kur} blocker	Several in *vitro* and in *vivo* animal models	under way	[36,37]
	DP01	Highly selective I_{Kur} blocker	Several in *vitro* and in *vivo* animal models	not	[38]
	Vernakalant	Primarily I_{Kr} and I_{Na} blocker, but additionally blocks I_{to}, I_{Na}, I_{Kr} and I_{Ks} (multichannel blocker)	Several in *vitro* and in *vivo* animal models	AVRO	[39,40]
	Ranolazine (FDA approval)	Primarily I_{Naf} and I_{NaL}, and I_{Kr} blocker, but additionally blocks I_{CaL} and I_{Ks} (multichannel blocker)	Several in *vitro* and in *vivo* animal models	MERLIN-TIMI 36	[41,42,43]
	NIP-142, NIP-152	Highly selective $I_{K,ACh}$ blockers	Several in *vitro* and in *vivo* animal models	not	[44,45]
NCX modulators	KB-R7943	Initially developed as selective NCX blocker, but additionally blocks I_{to}, I_{K}, I_{K1}, I_{Na}, and I_{CaL}	Several in *vitro* and in *vivo* animal models	not	[47]
	SEA-0400	Selective NCX blocker, but additionally blocks I_{CaL}	Several in *vitro* and in *vivo* animal models	not	[48,49]
Gap-junction therapy	Rotigaptide	Selective gap junction closer peptide	Several in *vitro* and in *vivo* animal models	not	[52,53]
	GAP-134	Selective gap junction closer peptide	Several in *vitro* and in *vivo* animal models	not	[54]

Table 1. New drugs and investigational compounds developed for treating AF.

structural remodelling, inflammation, and oxidative stress in development of AF is still not fully understood and varies significantly among different AF pathologies.

Conclusions

Great advances have been made in understanding the mechanisms underlying atrial remodelling and avenues of therapy in AF. Ongoing research aimed at developing novel pharmacological strategies for the management of AF includes both ion channel and non ion-channel mediated therapeutic approaches. However, while success to date has been modest, the recent identification of atrial- and pathology-selective targets and compounds able to directly modulate them hold promise for the development of effective treatment modalities. New antiarrhythmic drugs targeting multiple ion channels or possessing high affinity for atrial myocardium are believed to have a more favourable risk/benefit ratio than traditional antiarrhythmic drugs. Extensive studies utilising a wide range of such agents are currently underway with potentially promising results.

Acknowledgements

Supported by grants from OTKA (CNK-77855, K-82079), ETT (302-03/2009 and 306-03/2009), National Office for Research and Technology (NKFP_07_01-RYT07_AF and REG-DA-09-2-2009-0115), National Development Agency (TÁMOP-4.2.2.-08/1-2008-0013 and TÁMOP-4.2.1/B-09/1/KONV-2010-0005), EU-FP7 (ICT-2008-224381), HU-RO Cross-Border Cooperation Programmes (HURO/0901/137 and HURO/0802/011_AF) and the Hungarian Academy of Sciences.

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