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New pharmacological approaches to atrial fibrillation

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Atrial fibrillation (AF) is the most common cardiac arrhythmia facing physicians, afflicting 13% of men and 11% of women over 85 years of age. Epidemiological studies estimate that there are ≥11 million AF sufferers in the seven major economies and that its prevalence will increase two- to threefold over the next 50 years. Current strategies for treating AF involve either sinus rhythm (SR) maintenance or heart rate control, combined with anticoagulation therapy. Although SR control is the preferred and most effective treatment of AF, none of the SR control drugs currently available are able to maintain rhythm without significant side effects. In this article we discuss some of the recent advancements in developing new antiarrhythmic drugs for AF.

During the past decade or so, many of the new atrial fibrillation (AF) drugs that reached the clinical stages of drug development have worked by modulating multiple cardiac ion channels without excessively prolonging the QTc interval. Example drugs include dronedarone, vernakalant, AZD7009 and AVE0118 (Fig. 1). Because these drugs modulate cardiac ion channels present in the atria and ventricles they often have a narrow therapeutic index and in some cases are associated with life threatening safety issues [1]. An alternative approach to AF drug development is to selectively modulate ion channel targets present only in the atria. Although, this approach might provide AF drugs with attractive safety profiles, it remains to be demonstrated clinically whether they are as effective as multiple ion channel-blocking drugs, such as amiodarone in preventing recurrence of AF. Recent advances in the development of new AF drugs that target I_{Kur}, I_{KACh} or I_{Na} are discussed below.

I_{Kur} drugs

The voltage-gated potassium channel $K_v1.5$ underlies the cardiac ultra-rapid delayed-rectifier (I_{Kur}) current in humans [2,3] and is an attractive AF drug target because it is selectively expressed in human atria and not in the ventricles [4]. In atrial tissue from AF donors, inhibition of I_{Kur} extends the repolarisation phase of the atrial cardiac action potential (Fig. 2) to provide desirable antiarrhythmic effects without the risk of drug-induced *torsade de pointes*. This pathophysiological observation occurs because electrical and/or ion channel remodelling in AF patients increases the functional importance of potassium currents, such as I_{Kur} in early repolarisation [5]. However, there is some concern that I_{Kur} modulation alone will not be effective in treating AF because (i) I_{Kur} inactivates at the high frequencies experienced in AF [6], (ii) the I_{Kur} current is partially downregulated in AF patients [7], (iii) I_{Kur} inhibition shortens action potential duration (APD) in atrial tissue from sinus rhythm (SR) donors [5] (the opposite effect to that desired of an AF drug, which might even induce AF) and (iv) I_{Kur} inhibition might cause early afterdepolarisations in the presence of adrenergic stress [8,9]. However, the exact clinical relevance of these research findings remains to be determined. For example, it is known that although I_{Kur} is downregulated in AF tissue, inhibition of the remaining I_{Kur} current still significantly prolongs APD [5]. In addition to this, the relationship between APD and atrial effective refractory period (AERP) needs to be carefully evaluated in SR and AF human tissue at a range of frequencies relevant to atrial rates experienced during SR and AF. This is because changes in APD might not directly correlate with changes in AERP if the drug has additional effects on post-repolarisation refractoriness (PRR). Furthermore, the relevance of animal models to humans needs to be carefully considered, particularly for a single ion channel mechanism of action. For example, the physiological importance of I_{Kur},

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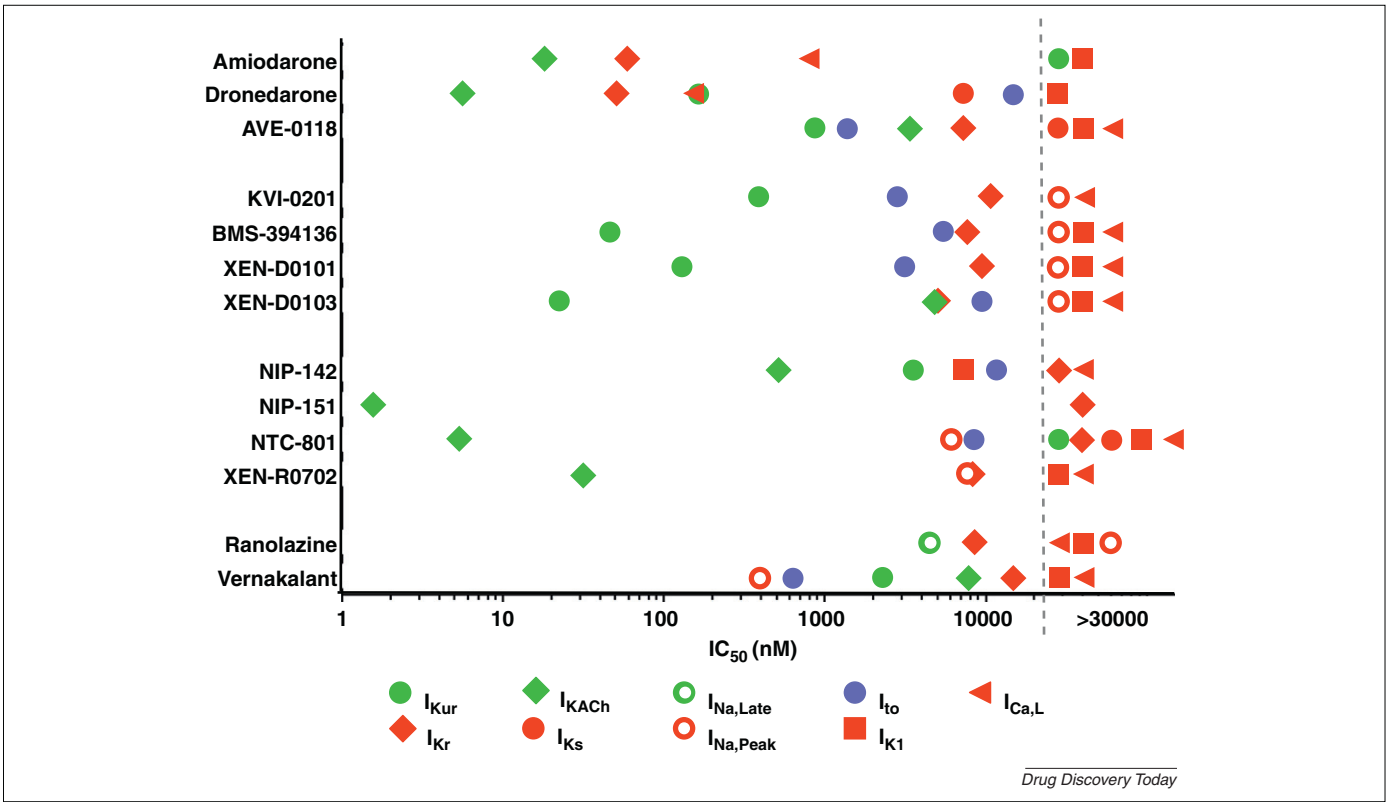

FIGURE 1

Ion channel pharmacology of the antiarrhythmic drugs. Drugs are grouped by their ion-channel selectivity with the upper most group being non-selective and/or mixed-ion channel modulators, beneath which are the selective I_{Kur} then I_{KACh} inhibitors with the atrial-selective I_{Na} inhibitors at the bottom. The IC_{50} values for each compound against either the native cardiac currents or their molecular correlate expressed in a recombinant mammalian (not *Xenopus*) system are plotted. Where multiple values exist in the literature the most potent value is presented. Care must be taken when comparing IC_{50} values from different laboratories because the value is dependent on several factors, including command waveform (voltage and frequency), temperature, expression system, ancillary subunits, species, in addition to technical consideration including tubing, buffer composition, among others. However, no single comparative study of these compounds has been published. IC_{50} values are presented as this is the most widely reported value for ion channel activity in the published literature and enables easy comparison. However, each current will contribute differently to the electrical properties of the physiological and pathological atria. As such prolongation of the action potential could be achieved by inhibition of a smaller percentage of inward rectifier channels than early-repolarising K_v channels. For some currents IC_{25} or indeed IC_{75} values might be more relevant when relating current inhibition to efficacy. Detailed human atria native current pharmacology at physiological temperature and voltage and at pathophysiologically relevant frequency are lacking to fully understand how ionic current inhibition relates to efficacy in humans.

the molecular correlate (which might not be $K_v1.5$ in all species), and the very high atrial rates observed during AF in animal models (*cf.* humans) causing I_{Kur} inactivation could all underestimate the efficacy of selective I_{Kur} drugs. Non-selective I_{Kur} modulating drugs evaluated in the clinic include vernakalant and AVE0118. Only four selective I_{Kur} drugs have entered development (as discussed below).

BMS-394136 [Bristol-Myers Squibb (BMS) and Icagen]

BMS-394136 inhibits $K_v1.5$ (IC_{50} 50 nM), is at least 150-fold selective over I_{Kr}, I_{Ks}, I_{Ca}, and I_{to} [10] and selectively increases the AERP in rabbit and dog [11]. BMS-394136 (100 mg, oral solution) has been evaluated in a clinical pharmacodynamic study to determine its electrophysiological effects on the atrium and ventricle in patients with dual-chamber pacemakers or defibrillators (ClinicalTrials.gov identifier: NCT00162448). However, results from this particular study have not been reported and the current clinical status BMS-394136 is unknown.

KVI-0201/WYE-160020 (Procter & Gamble/Wyeth)

KVI-0201 inhibits $K_v1.5$ (IC_{50} 50 nM) and is eightfold selective over $K_v4.3$, 30-fold selective over **h**uman **E***ther-à-go-go*-**R**elated **G**ene (hERG) and >500× selective over $Na_v1.5$, $Ca_v1.2$ and $Ca_v1.3$ [12]. Intravenously dosed KVI-0201 selectively increased AERP and repeated oral doses of KVI-0201 significantly reduced AF inducibility and burden in dog, although unbound drug plasma concentrations were significantly below the $K_v1.5$ IC_{50} value [12]. KVI-0201 has been selected as a development candidate but the current clinical status of this compound is unknown.

XEN-D0101 (Xention)

XEN-D0101 inhibits human I_{Kur} (IC_{50} 154 nM) and is 60-fold selective over I_{to} and ≥80-fold selective over hERG and $Na_v1.5$ [13]. XEN-D0101 prevented AF and selectively increased AERP in two different dog AF models [14,15]. Although XEN-D0101 has been evaluated in two separate clinical studies (data unreported), development activities have ceased as Xention (http://www.xention.com/) has switched to developing XEN-D0103.

XEN-D0103 (Xention)

XEN-D0103 inhibits $K_v1.5$ (IC_{50} 25 nM) and is ≥250-fold selective over non-target cardiac channels ($K_{ir}3.1/3.4$, hERG, $K_v4.3$, $K_{ir}2.1$, $Ca_v1.2$, $Na_v1.5$ and $K_v7.1$) [16]. Intravenously dosed XEN-D0103 increased AERP and prevented AF without producing undesirable changes in QTc interval, heart rate (HR) or blood pressure in

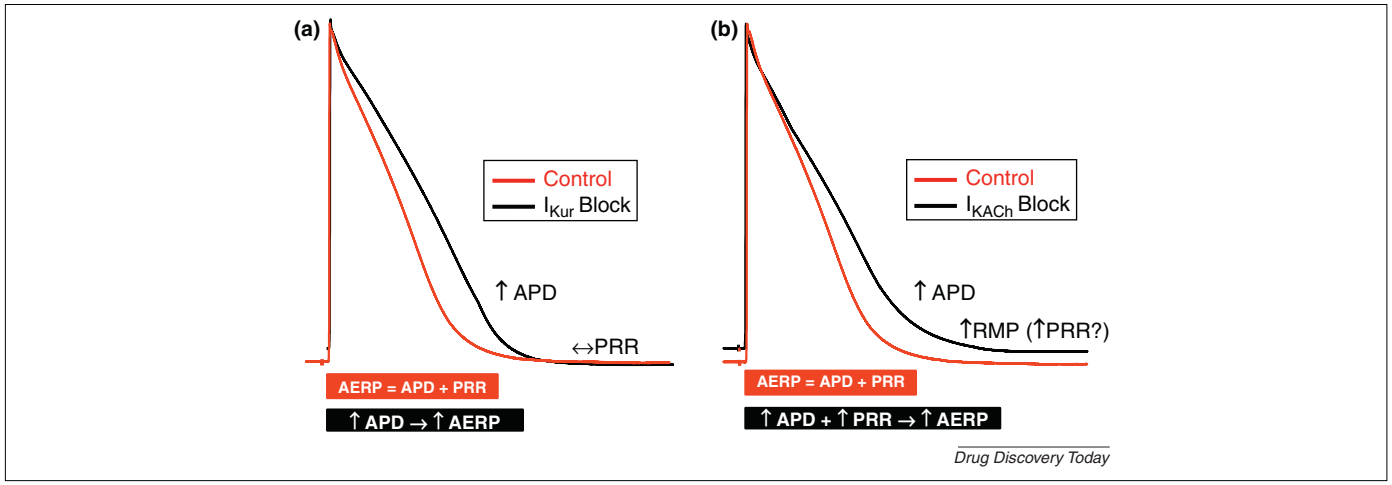

FIGURE 2

The effect of selectively inhibiting I_{Kur} **(a)** or I_{KACh} **(b)** on the human atrial action potential. The rationale for design of selective potassium channel blockers is to prolong the atrial AERP, reducing the ability of the atria to sustain re-entrant arrhythmias. The AERP is a function of APD plus the PRR period. PRR is most probably determined by Na^+ channel availability. Selective inhibition of the voltage-dependent delayed-rectifier current, I_{Kur}, is expected to reduce potassium conductance at more positive potentials resulting in prolongation of the early repolarisation of the action potential with perhaps less effect on late repolarisation. Selective I_{Kur} inhibition would not be expected to affect the RMP or PRR. By contrast, selective inhibition of the inwardly rectifying current, I_{KACh}, would be expected to have less effect on early repolarisation of the action potential, and have greater effect on the terminal phase of repolarisation at more negative potentials. Furthermore the contribution of I_{KACh} (which is constitutively active in chronic AF) to maintaining the RMP (along with I_{K1}) would also result in a depolarisation of the RMP which is turn may reduce Na^+ channel availability and increase PRR. This could also translate in to reduction in dV/dt of the action potential upstroke. This indirect effect on Na^+ channel availability may reduce automaticity and prevent the atria from sustaining AF rotors. It can be hypothesised that the effect of I_{KACh} inhibitors to both terminate and prevent AF in several animal models may result from their direct effects on AERP and their indirect effects on Na^+ channels. By contrast animal models suggest that I_{Kur} blockers are less effective at termination and may be better suited to the prevention of recurrence of AF. *Note*: the action potential profile in AF is abbreviated and triangulated owing to the down- and upregulation of ionic currents. *Abbreviations*: AERP: atrial effective refractory period; AF: atrial fibrillation; APD: action potential duration; PRR: post-repolarisation refractoriness; RMP: resting membrane potential.

atrial-tachypaced dogs [16]. XEN-D0103 is currently being evaluated in a Phase I clinical study to assess the pharmacokinetics, safety and tolerability of single and repeat dosing. A Phase II clinical proof-of-concept study will commence in 2012.

I_{KACh} drugs

The acetylcholine-activated inward rectifier potassium current (I_{KACh}) is found predominantly in the supraventricular regions and conduction (Purkinje) system of the heart. Conducting I_{KACh} is a heterotetrameric channel composed of $K_{ir}3.1/3.4$ subunits [17,18]. Activation of this current shortens the atrial APD and AERP and reduces the rate of diastolic depolarisation in nodal tissues (negatively chronotropic and dromotropic). Additionally, I_{KACh} is a strong inward rectifier that contributes to stabilising the resting membrane potential (RMP). Inhibition of I_{KACh} is expected to both prolong APD and/or AERP and depolarise the RMP (Fig. 2). Increased activity of I_{KACh} through vagal-activation [19] or constitutive-activation through post-translational modification [20], could be important factors in the induction and maintenance of AF by abbreviation of the APD and/or AERP, hyperpolarisation of the RMP and promotion of electrical heterogeneity in the atria, increasing the risk of re-entrant arrhythmias. Constitutive I_{KACh} has been reported in the right and left atria of patients with chronic AF [20–22] and the left atria in paroxysmal AF [22], suggesting I_{KACh} inhibitors might be effective in both these patient populations. Analysis of HR variability suggests that vagal-tone might also be an important factor in paroxysmal AF. However, the role of vagal-tone in paroxysmal AF is often inferred from the context of the AF initiation (e.g. paroxysms that occur at night or post-eating). It is known that ablation is most effective in paroxysmal AF where damaging ganglionic plexi and parasympathetic (and sympathetic) denervation might contribute to its efficacy however this remains debated. Parasympathetic drive is not a prevalent cause of paroxysmal AF but might be important in younger patients and in the absence of structural heart disease. Selective I_{KACh} inhibitors will help understand the contribution of the parasympathetic system and constitutive I_{KACh} to the initiation and perpetuation of AF. Beyond effects on the atria, constitutive-activation of I_{KACh} in the pulmonary sleeve of atrial-tachypaced dogs might have an important role in initiating AF triggers [23]. Clinical trials such as those being conducted with NTC-801 will aid in defining the target AF population. Although I_{KACh} as a target for AF is considerably less well explored than I_{Kur}, two compounds have reached clinical development and several are in preclinical development.

NIP-142 and NIP-151 (Nissan)

NIP-142 provided the first *in vivo* evidence that a moderately potent and selective small molecule I_{KACh} inhibitor can terminate vagal- [vagus nerve stimulation (VNS)] and aconitine-induced (AI) AF and flutter (AFL) in the dog. Despite its polypharmacology this compound exerted a relatively atrial-selective effect on the heart [24]. The second generation NIP-151, displayed superior potency for I_{KACh} and selectivity over hERG and represents the first highly selective small molecule I_{KACh} inhibitor, although data on other cardiac ion channels are lacking. Similar to NIP-142 it was effective in both the VNS and AI models at terminating AF in addition to preventing re-induction in the VNS model. Intravenous infusion up to ten times the maximal effective dose had no effect on electrocardiography (ECG) parameters (HR, QRS, QTc) [25]. It is unclear whether these compounds entered clinical development.

NTC-801/BMS-914392 (Nissan/Teijin/BMS)

The third generation compound, co-developed with Teijin (http://www.teijin.co.jp/english/) in Japan and BMS (www.bms.com) outside Japan,

NTC-801 (BMS-914392), is the first selective I_{KACh} inhibitor to be tested in humans, and inhibits I_{KACh} with an IC_{50} of 5.7 nM, displaying over 1000-fold selectivity over other cardiac channels [26]. Similar to NIP-142 and 151, it is effective in terminating VNS/AI AF in the dog. NTC-801 was also the first selective I_{KACh} inhibitor to be shown to prevent the induction of AF in an atrial-tachypacing dog model of persistent AF (AT-AF) in which the atria exhibits electrical remodelling akin to chronic AF in humans. NTC-801 is currently in two Phase II efficacy studies. The first trial in Japan (announced April 2009) is to investigate the effect of NTC-801 in the maintenance of SR in a patient population with persistent AF. The second Phase II trial (started May 2011 in the UK) will assess the effects of NTC-801 on AF burden, HR and QTc in paroxysmal AF patients (ClinicalTrials.gov identifier: NCT01356914, www.clinicaltrials.gov/ct2/show/NCT01356914). The need to dose Three times daily (TID) in one of these Phase II trials might suggest a short half-life and the requirement for a sustained release formulation.

AZD-2739 (AstraZeneca)

AstraZeneca has entered Phase II (ClinicalTrials.gov identifier: NCT01396226, www.clinicaltrials.gov/ct2/show/NCT01396226) with an I_{KACh} inhibitor to assess the effects on atrial and ventricular refractoriness and other ECG parameters following Intravenous infusion in patients with a history of AFL and/or AF. No data on the ion-channel selectivity profile of this drug have been published.

XEN-R0702 (Xention)

Xention has presented data on an advanced lead compound XEN-R0702. This compound has low nanomolar potency for $K_{ir}3.1/3.4$ and $\geq$300-fold selectivity for hERG and other cardiac ion channels. XEN-R0702 was shown to prolong the human atrial action potential in AF and SR tissue and to be effective in the AT-AF dog model without effect on QTc, HR or BP parameters in conscious animals [27].

Several questions remain regarding the safety of targeting I_{KACh} and/or $K_{ir}3.1/3.4$. Preclinical data and early Phase I clinical data [NTC-801, AZD-2739 (unpublished)] suggest inhibition of I_{KACh} is well tolerated, and perhaps surprisingly, has little effect on HR [26,27]. Knockout of the *KCNJ5* gene in mice had no effect on resting HR but it did alter HR variability [28]. This is consistent with data from the (anaesthetised and conscious) dog where HR was unchanged following dosing of selective I_{KACh} inhibitors [26,27]. During AF, slow atrioventricular node (AVN) conduction acts as a high-frequency filter, limiting ectopic electrical activity from the atria activating the ventricles. Increasing AVN conduction through inhibition of I_{KACh} could cause increased ventricular rate and result in tachy-induced cardiomyopathy. It should be noted that in the Xention study the AVN was not ablated and XEN-R0702 did not increase ventricular rate in conscious AT-AF dogs at doses up to 10 mg/kg, in a species reported to have high vagal-tone. Given that increased HR and altered HR variability are associated with negative clinical outcome and mortality, clinical assessment of these parameters are important.

Although parasympathetic innervation to the Purkinje system is less apparent than the sympathetic system, acetylcholine has been shown to hyperpolarise and decrease the automaticity of dog Purkinje fibres. Inhibition of I_{KACh} and depolarisation of the RMP could lead to increased abnormal automaticity in the Purkinje system and potentially lead to tachycardia and/or arrhythmia. However, no ventricular arrhythmia has been reported in any of the *in vivo* studies performed in the dog with selective I_{KACh} inhibitors [24–29]. A sound physiological rationale exists for other cardiac effects; however redundancy and a compensatory role of other currents or remodelling that might occur in these tissues in AF and species differences also need to be considered.

Targeting $K_{ir}3/1.3.4$ might also result in other non-cardiac effects. Peripherally [non-central nervous system (CNS)], the co-expression of $K_{ir}3.1$ and $K_{ir}3.4$ is predominantly in the heart. However, $K_{ir}3.1$ and $K_{ir}3.4$ protein were detected in human retinal pigment epithelium [30] and $K_{ir}3.4$ has been reported in the pancreas [31] in humans and in adrenal glomerulus cells where two somatic mutations result in altered ion selectivity causing hyperaldosteronism and hypertension [32]. It is unclear whether the protein is expressed as a homo- or heterotetramer in these tissues and what the functional consequences of inhibiting it will be. In the pancreas it might be a $K_{ir}3.2/3.4$ heterotetramer [33] which would be expected to have markedly different pharmacology to $K_{ir}3.1/3.4$. Owing to the expression of K_{ir} ion channels in the CNS, it will be essential to ensure that any I_{KACh} inhibitor does not penetrate the CNS to avoid undesirable neurological side effects.

I_{Na} drugs

While inhibition of the potassium currents described in the preceding sections act to prevent AF by prolonging the atrial APD, an alternate mechanism involves inhibition of cardiac sodium currents to reduce excitability and promote PRR (Fig. 2). In fact many of the agents that have found usefulness in the treatment of AF include block of the cardiac sodium current among their multiple mechanisms and in some cases this might be their most significant activity. Amiodarone demonstrates an atrial-selective reduction in the maximal rate of rise of the action potential upstroke, prolongs conduction time and induces PRR, all likely to be mediated by sodium channel block [34]. AZD7009 slows conduction velocity and decreases excitability in the atrium, perhaps as a result of its ability to block I_{Na} more potently than I_{Kr} and I_{Kur} [35]. Similarly vernakalant blocks I_{Na} more potently than the various potassium currents that this multi-channel blocker also inhibits [36]. A further potential AF drug, vanoxerine, displays a slightly different profile with sub-micromolar sodium channel block combined with even more potent hERG block [37]. It remains to be seen whether the relatively atrial-selective action of these molecules is driven, at least in part, by their non-selective profile and that perhaps a delicate balance of I_{Na} and I_{Kr} block is beneficial, or even essential, for efficacy and safety in this class of compounds; as more selective molecules are identified this might become clearer.

To have a satisfactory safety profile sodium channel-blocking drugs must demonstrate more significant effects in the atria compared with the ventricles. To date there is no evidence for the atrial and ventricular sodium channels being different at the molecular level. Nevertheless sodium channel blockers have been found to display a wide range of selectivity profiles, from the apparently ventricle-selective nature of mexiletine and tedisamil, through non-selective antagonists, such as lidocaine and propafenone, to apparently atrial-selective antagonists, such as amiodarone. Atrial selectivity of action is likely to be the result of the ability of a molecule to take advantage of the biophysical differences that exist between atrial and ventricular cardiac myocytes and the individual and composite ion channel currents that characterise their respective functions. Differences in RMP and voltage-dependence of activation and/or inactivation have been demonstrated, and it is recognised that recovery of sodium channels from the inactivated state is slower in atrial cells. Phase III repolarisation is also slower in the atrium compared with the ventricle, a factor that is made more significant for those molecules that also block I_{Kr}. Many of the compounds that have demonstrated atrial selectivity appear to target the inactivated state of the sodium channel, whose population might be expected to be

increased in the atria compared with the ventricles as a result of the higher RMP and more negative half-inactivation voltage, however it is also probably that the mixed-ion channel-blocking nature of these drugs contributes substantially to their efficacy. Clinical data with relatively selective compounds, such as lidocaine and mexiletine suggest that block of I_{Na} alone will not be sufficient to suppress AF.

A further possible route to atrial selectivity was recently described for the anti-anginal drug ranolazine, which was shown to be selective for the preopen and/or open state of the sodium channel, a mechanism that might also lend a degree of selectivity for the late phase of the cardiac sodium current, which is suggested to be beneficial in treating AF [38]. Studies with this molecule suggest that the open-state block is complemented by fast unbinding from closed channels. In canine atria, ranolazine demonstrated the potential to prevent induction of AF and to terminate AF [39], and clinical evidence for the anti-AF properties of ranolazine came from meta-analysis of the MERLIN-TIMI36 trial [40]. Other retrospective analysis suggested ranolozine treatment was associated with a lower incidence of post-operative AF compared with amiodarone [41]. Ranolazine is currently in clinical studies to determine its usefulness in reducing the incidence of recurrence of AF after electrical cardioversion of persistent AF (Clinicaltrials.gov Identifier: NCT01349491, www.clinicaltrials.gov/ct2/show/NCT01349491) and also to determine whether ranolazine can suppress AF following cardiac surgery (Clinicaltrials.gov Identifier: NCT01352416, www.clinicaltrials.gov/ct2/show/NCT01352416). Ranolazine is not approved for the treatment of AF and has not undergone a randomised placebo controlled trial for this indication. Of note, vernakalant slows down conduction velocity specifically in atria, pointing to its atrial selectivity in blocking peak I_{Na} [42].

Concluding remarks

Although encouraging preclinical data have been reported for all three mechanisms discussed in this article, they all essentially remain clinically unproven for maintaining SR. This is because (i) many of the currently approved AF drugs display polypharmacology for cardiac ion channels thus making it impossible to assess the potential clinical value of modulating single ion channel targets in the atria from these data, (ii) selective I_{Kur}, I_{KACh} or I_{Na} drugs have not yet been evaluated in Phase II efficacy clinical trials and (iii) there is a lack of truly selective I_{Na} drugs that only modulated voltage-gated sodium channels in the atria.

The clinical evaluation of atrial-selective drugs will not only answer important questions about which mechanism provides superior efficacy but it will also determine if one is also associated with a particular safety concern. Although it is believed that single ion channel modulation will be sufficient to prevent the recurrence of AF, it will be interesting to determine whether combining single ion channel drugs provide additive or synergistic pharmacodynamic effects in the atria. Such an approach could provide more personalised care in a highly heterogeneous population.

In conclusion, drugs which modulate single ion channel targets in the atria are likely to have superior safety profiles to existing AF drugs. Although no preference is given to the three targets discussed. A potential advantage of I_{Kur} and I_{KACh} over I_{Na} is that these two targets represent atrial specific single ion channels targets not found in the ventricle. Furthermore, the target product profile and/or mechanism of action for an atrial-selective I_{Na} drug needs to be validated and perhaps it might even be unachievable to modulated only Na^+ channels in the atria, especially in diseased patients with electrically and structurally remodelled hearts.

Conflict of interest

JM, DM and JF are all employees of Xention and either hold shares or options in Xention Ltd.

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