Atrial fibrillation (AF) is the most common cardiac arrhythmia and the occurrence ofAF increases with age. The prevalence of AF rises from 0.5% in people in their 50s to 5% in people over the age of 65 years. This rises to nearly 10% in the octogenarian population. AF is a major cause of morbidity and mortality, increasing the risk of death, congestive heart failure (CHF) and embolic phenomena, including stroke. It is believed that AF is a lifetime risk in the ageing population and it is emerging as a major public health concern. The management of AF includes surgery, ablation and pharmacological therapies. However, only some cases are amenable to surgical or ablative therapies, and most of them require antiarrhythmic drug treatment. Over the years, delayed rectifier K+ currents (IK), especially to surgical or ablative therapies, and most of them require antiarrhythmic drugs. Blockade of these ion channels (class III antiarrhythmic drugs) leads to a prolongation of atrial and ventricular action potential duration (APD) and the refractory period, which is the desired antiarrhythmic effect. However, prolongation of ventricular repolarisation causes a prolongation of the QT interval and an increased propensity for life-threatening ventricular arrhythmias. Therefore, there is a clear need to develop new drugs that may act mainly on electrical activity in the atrium of the human heart to prevent or treat AF.

Recent Advances in the Development of Selective Anti-atrial Fibrillation Drugs

**a report by**

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Atrial-specific ion channel blockers

The pharmaceutical industry has recently made great progress in the development of new antiarrhythmic drugs to treat AF. The design of selective anti-AF drugs pays more attention to compounds that block the atrial-specific Ikur and/or IKACh. It is believed that one of the feared side effects of class III drugs – torsades de pointes arrhythmias – can be overcome by developing a drug that lengthens only the duration of the atrial action potential without increasing the QT interval. Moreover, the dose of the drug needed for effectiveness will be less limited. Several compounds that block hKv1.5 channels and/or native Ikur have been developed by Aventis. S9947 (2’-benzyl-oxycarbonyl-aminomethyl)biphenyl-2-carboxylic acid 2-(2-pyridyl)ethyamide) and S20951 (2’-[2-(4-methoxyphenyl)-acetylamino]-methyl-biphenyl-2-carboxylic acid 2,4-difluoro-benzylamide) showed remarkable blocking effects on Kv1.5 channel currents expressed in Xenopus oocytes and Chinese hamster ovary (CHO) cells, and on Ikur in human atrial and rat cardiomyocytes. In vivo experiments demonstrated that both S9947 and S20951 significantly prolonged the left atrial refractory period in pigs.

AVE0118 (2’-[2-(4-methoxy-phenyl)-acetylamino]-methyl-biphenyl-2-carboxylic acid (2-pyridinyl-3-yl-ethyl)-amide) is a well-studied Ikur blocker developed by Aventis from computationally designed chemical compounds with a structure-based virtual screening procedure for Kv1.5 block. This compound was initially found to inhibit human atrial Ikur and Ito, and the inhibitory effect on IKACh was then demonstrated in pig atrial myocytes. AVE0118 showed a slight suppression of Ikur, Ito and Icain in
guinea pig cardiac myocytes.19 In addition, AVE0118 was found to significantly prolong the atrial refractory period and completely prevent vulnerability to AF induced by extra stimuli in pigs.20 Importantly, this compound showed excellent anti-AF action in a chronic AF goat model.21 A phase II clinical trial of AVE0118 is under way. NIP-141 and NIP-142 are novel benzopyran derivatives developed by Nissan Chemicals. They inhibit human atrial I\textsubscript{Kur} and I\textsubscript{Ca,L}.22 It was experimentally demonstrated that NIP-142 had an inhibitory effect on I\textsubscript{Kur} in guinea pig atrium23 and suppressed AF and atrial flutter in a dog model.24 Effects of NIP-141 or NIP-142 on other cardiac ion channels remain undetermined.

A series of diphenyl phosphine oxide (DPO) is a type of potent I\textsubscript{Kur} blocker developed by Merck. These compounds inhibited hKv1.5 with IC\textsubscript{50}s less than micromolar, suppressed human atrial I\textsubscript{Kur} without affecting I\textsubscript{Na}, prolonged human atrial action potential and showed a weak inhibitory effect on I\textsubscript{Kur} and I\textsubscript{K1} in guinea pig ventricular myocytes.25 DPO-1 was found to significantly prolong the atrial refractory period in non-human primates without prolonging QTc interval26 and to terminate atrial flutter in a dog model.27 Another important I\textsubscript{Kur} blocker recently patented by the authors of this article28,29 is a natural flavone compound (Compound A, 5,7-dihydroxy-4’-methoxyflavone). Compound A was initially discovered in traditional Chinese medicine: Xuelianhuang (Saussurea tridactyla). The compound is distributed in plant pigments, universally present in vascular plants and responsible for many of the colours in nature.30 The flavone compounds have been demonstrated to be strong antioxidants that occur naturally in foods and can inhibit carcinogenesis.31,32 Our study showed that, remarkably, Compound A inhibited I\textsubscript{Kur} and I\textsubscript{K1} in human atrial myocytes and I\textsubscript{Kur} in guinea pig atrial myocytes and showed a weak inhibition of human cardiac I\textsubscript{Kur} and hERG channels expressed in HEK 293 cells. It had no effect on I\textsubscript{K1}, I\textsubscript{Kur} and I\textsubscript{Ca,L}. Importantly, this compound was found to effectively prolong the atrial refractory period in anaesthetised dogs after intra-duodenal administration without blocking QTc prolongation. Anti-AF study of Compound A is under way.

Multiple Channel Blockers

The Na\textsuperscript{+} channel blockader is believed to be highly effective in terminating AF by causing primary re-entry waves.33 Therefore, the I\textsubscript{Na} blocking effect is likely beneficial for a compound that selectively blocks atrial K\textsuperscript{+} channels. RSD1235 (vernakalant) is a new antiarrhythmic agent developed by Cardiome. Vernakalant showed multiple ion channel-blocking effects, including properties of frequency-dependent Na\textsuperscript{+}-channel blockade and atrial-preferential potassium-channel (I\textsubscript{Kur} and I\textsubscript{Ito}) blockade.34 This compound has been evaluated as an intravenous agent for acute conversion of AF. At a dose of 3mg/kg followed by another 2mg/kg after 15 minutes, vernakalant resulted in 52% conversion of new-onset AF versus 4% with placebo. There was no evidence of QT prolongation or proarrhythmia.35 AZD7009 is a new antiarrhythmic agent developed by AstraZeneca. This compound showed both Na\textsuperscript{+} and K\textsuperscript{+} (hERG and I\textsubscript{IKACh}) current blocking properties.36 In a canine model, AZD7009 terminated AF and flutter and prevented re-induction. Atrial refractoriness was prolonged to a greater degree than ventricular refractoriness (33 versus 17%) and QT prolongation was modest.37 A recent phase II dose-dependent study demonstrated that AZD7009 resulted in acute conversion in patients with recent onset of AF or flutter. QT prolongation was also observed.38 Therefore, caution is advised when using this compound.

Perspective

A number of promising atrial-specific drugs have been developed from chemically synthesised compounds or natural compounds for anti-AF. Hopefully, it will mark the beginning of a clinically exciting time in anti-AF testing. Despite the advances of numerous alternatives, pharmaco-therapeutic treatment of AF will prevail in the near future.