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

a report by
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Atrial fibrillation (AF) is the most common cardiac arrhythmia and the occurrence of AF 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.[1] AF is a major cause of morbidity and mortality, increasing the risk of death, congestive heart failure (CHF) and embolic phenomena, including stroke.[1] It is believed that AF is a lifetime risk in the ageing population[2] and it is emerging as a major public health concern.[3] The management of AF includes surgery, ablation[4,5] and pharmacological therapies.[6] However, only some cases are amenable to surgical or ablative therapies, and most of them require antiarrhythmic drug treatment.[6] Over the years, delayed rectifier K^+ currents (I_K), especially the rapidly-activating I_K (I_{Kr}, encoded by hERG, ether-a-go-go gene), have been important targets for 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.[7,8] However, prolongation of ventricular repolarisation causes a prolongation of the QT interval and an increased propensity for life-threatening ventricular arrhythmias.[9] 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.

Ion Channel Currents in the Atrium and Ventricle of the Human Heart

It is well-known that human cardiac APD and the refractory period generally depend on the balance of inward and outward currents in atrial and ventricular myocytes (see *Figure 1*). Inward currents include the Na^+ current (I_{Na}) and L-type Ca^{2+} current ($I_{Ca.L}$), and outward currents include the transient outward K^+ current (I_{to}), I_{Kr} and slowly-activating delayed rectifier K^+ current (I_{Ks}) and inward rectifier K^+ current (I_{K1}). In general, I_{Na} channel activation depolarises cell membrane and initiates action potential (phase 0), then I_{to} activation forms a fast repolarisation (phase 1). Activation of $I_{Ca.L}$ maintains the plateau of the action potential

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(phase 2); I_{Kr} and I_{Ks} gradually activate and induce slow repolarisation during phase 2. Finally, activation of I_{K1} channels induces final repolarisation (phase 3) and maintains resting membrane potential (phase 4). The electrogenic $Na^+–Ca^{2+}$ exchanger mainly carries an inward current and also plays a role in maintaining the plateau of cardiac action potential.

It is interesting that ultrarapidly activating delayed rectifier K^+ channel (encoded by Kv1.5 gene) current (I_{Kur}) was found to be functionally present in the atrium[10] but not in the ventricle of the human heart.[11] It is important for human atrial repolarisation. In addition, acetylcholine-activated K^+ channels (I_{KACh}, mediated by muscarinic receptors) are dominantly distributed in the atrium of the human heart and also contribute to human atrial repolarisation (see *Figure 1*). It has recently been reported that $I_{K.ACh}$ and muscarinic receptor expression are upregulated in AF patients[12] and in AF induced in experimental dogs with heart failure.[13] Therefore, blockage of I_{KACh} could terminate AF induced by the increased vagal nerve tone. It is believed that blockade of atrial K^+ channels (I_{Kur} and/or I_{KACh}) could provide an approach for the control of atrial arrhythmias without adverse ventricular effects. Therefore, the compounds targeted to I_{Kur} and/or I_{KACh} would be promising agents for developing selective anti-AF drugs.

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 I_{Kur} and/or I_{KACh}.[14,15] 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 I_{Kur} have been developed by Aventis. S9947 (2'-(benzyloxycarbonylaminomethyl) biphenyl-2-carboxylic acid 2-(2-pyridyl)ethylamide) 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 I_{Kur} in human atrial and rat cardiomyocytes.[16] *In vivo* experiments demonstrated that both S9947 and S20951 significantly prolonged the left atrial refractory period in pigs.[17]

AVE0118 (2'-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide) is a well-studied I_{Kur} blocker developed by Aventis from computationally designed chemical compounds with a structure-based virtual screening procedure for Kv1.5 block.[18] This compound was initially found to inhibit human atrial I_{Kur} and Ito, and the inhibitory effect on I_{KACh} was then demonstrated in pig atrial myocytes. AVE0118 showed a slight suppression of I_{Ks}, I_{Kr} and $I_{Ca.L}$ 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_{Kur} and I_{to}.[22,23] It was experimentally demonstrated that NIP-142 had an inhibitory effect on I_{KACh} in guinea pig atrium[24] and suppressed AF and atrial flutter in a dog model.[25] 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_{Kur} blocker developed by Merck. These compounds inhibited hKv1.5 with IC_{50}s less than micromolar, suppressed human atrial I_{Kur} without affecting I_{to}, prolonged human atrial action potential and showed a weak inhibitory effect on I_{K1} and I_{Ks} in guinea pig ventricular myocytes.[26] DPO-1 was found to significantly prolong the atrial refractory period in non-human primates without prolonging QTc interval[27] and to terminate atrial flutter in a dog model.[28] Another important I_{Kur} blocker recently patented by the authors of this article[29,30] is a natural flavone compound (Compound A, 5,7-dihydroxy-4'-methoxyflavone). Compound A was initially discovered in traditional Chinese medicine: Xuelianhua (*Saussurea tridactyla*). The compound is distributed in plant pigments, universally present in vascular plants and responsible for many of the colours in nature.[31] 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_{Kur} and I_{to} in human atrial myocytes and I_{KACh} in guinea pig atrial myocytes and showed a weak inhibition of human cardiac I_{Ks} and hERG channels expressed in HEK 293 cells. It had no effect on I_{K1}, I_{Na} and $I_{Ca.L}$. 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^+-channel blockade is believed to be highly effective in terminating AF by causing primary re-entry waves.[33] Therefore, the I_{Na} blocking effect is likely beneficial for a compound that selectively blocks atrial K^+ channels. RSD1235 (vernakalant) is a new antiarrhythmic agent developed by Cardiome. Vernakalant showed multiple ion channel-blocking effects, including properties of frequency-dependent Na^+-channel blockade and atrial-preferential potassium-channel (I_{Kur} and I_{to}) 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

Figure 1: Distribution of Ion Channel Currents Corresponding to the Atrial and Ventricular Action Potentials of the Human Heart
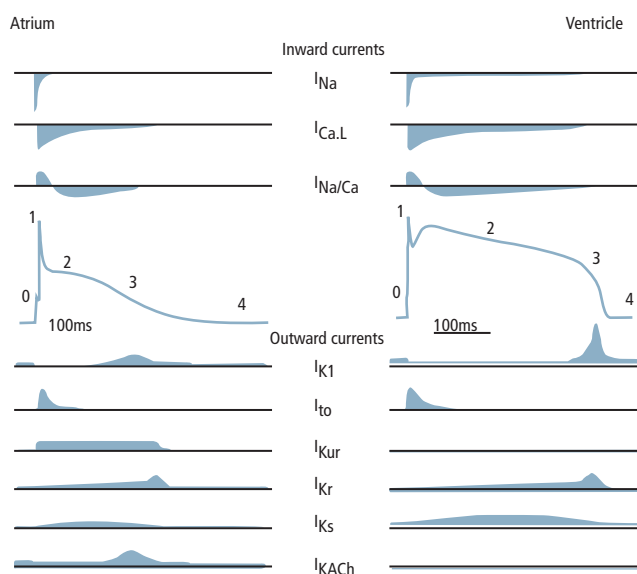
Specified pacemaker and conducting tissues not included. I_{Na}, Na^+ channel current; $I_{Ca.L}$, L-type Ca^{2+} current; $I_{Na/Ca}$, Na^+-Ca^{2+} exchanger current; I_{K1}, inward rectifier K^+ current; I_{to}, transient outward K^+ current; I_{Kur}, ultrarapidly activating delayed rectifier K^+ current; I_{Kr}, rapidly activating delayed rectifier K^+ current; I_{Ks}, slowly activating delayed rectifier K^+ current; I_{KACh}, acetylcholine-activated K^+ current. I_{Kur} and I_{KACh} are functionally present in the atrium but not in the ventricle of human heart.

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^+ and K^+ (hERG and I_{Ks}) 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, pharmacological treatment of AF will prevail in the near future. ■

1. Stewart S, Hart CL, et al., *Am J Med*, 2002;113:359–64.
2. Lloyd-Jones DM, Wang TJ, Leip EP, et al., *Circulation*, 2004;110:1042–6.
3. Braunwald E, *N Engl J Med*, 1997;337:1360–69.
4. Jahangiri M, Weir G, et al., *Ann Thorac Surg*, 2006;82:357–64.
5. Riley MJ, Marrouche NF, *Curr Probl Cardiol*, 2006;31:361–90.
6. Nattel S, Khairy P, Roy D, et al., *Drugs*, 2002;62:2377–97.
7. Sharma PP, Sarma JS, Singh BN, *J Cardiovasc Pharmacol Ther*, 1999;4:15–21.
8. Nattel S, Singh BN, *Am J Cardiol*, 1999;84:11–19R.
9. Roden DM, Anderson ME, *Handb Exp Pharmacol*, 2006;73–97.
10. Wang Z, Fermini B, Nattel S, *Cardiovasc Res*, 1994;28:1540–46.
11. Li GR, Feng J, Yue L, et al., *Circ Res*, 1996;78:689–96.
12. Bosch RF, et al., *Cardiovasc Res*, 1999;44:121–31.
13. Shi H, Wang H, et al., *Cell Physiol Biochem*, 2004;14:31–40.
14. Peukert S, Brendel J, Pirard B, et al., *J Med Chem*, 2003;46:486–98.

15. Pecini R, Elming H, Pedersen OD, et al., *Expert Opin Emerg Drugs*, 2005;10:311–22.
16. Bachmann A, Gutcher I, Kopp K, et al., *Naunyn Schmiedebergs Arch Pharmacol*, 2001;364:472–8.
17. Knobloch K, Brendel J, Peukert S, et al., *Naunyn Schmiedebergs Arch Pharmacol*, 2002;366:482–7.
18. Pirard B, Brendel J, Peukert S, *J Chem Inf Model*, 2005;45:477–85.
19. Gogelein H, Brendel J, Steinmeyer K, et al., *Naunyn Schmiedebergs Arch Pharmacol*, 2004;370:183–92.
20. Wirth KJ, Paehler T, Rosenstein B, et al., *Cardiovasc Res*, 2003;60:298–306.
21. Blaauw Y, Gogelein H, et al., *Circulation*, 2004;110:1717–24.
22. Matsuda T, Masumiya H, et al., *Life Sci*, 2001;68:2017–24.
23. Seki A, et al., *J Cardiovasc Pharmacol*, 2002;9:29–38.
24. Matsuda T, et al., *J Pharmacol Sci*, 2006;101:303–10.
25. Nagasawa H, Fujiki A, et al., *Circ J*, 2002;66:185–191.

26. Lagrutta A, Wang J, et al., *J Pharmacol Exp Ther*, 2006;317:1054–63.
27. Regan CP, et al., *J Pharmacol Exp Ther*, 2006;316:727–32.
28. Stump GL, et al., *J Pharmacol Exp Ther*, 2005;315:1362–7.
29. Li GR, CardioRhythm – Hong Kong Proceedings, 2007; abstract 10.
30. Li GR, Qin GW, et al., *Prog Clin Biol Res*, 1988;280:29–44.
32. Liu ZQ, Luo XY, Sun YX, et al., *J Pharm Pharmacol*, 2004;56:1557–62.
33. Kneller J, Kalifa J, Zou R, et al., *Circ Res*, 2005;96:e35–47.
34. Fedida D, et al., *J Cardiovasc Electrophysiol*, 2005;16:1227–38.
35. Roy D, et al., *J Am Coll Cardiol*, 2004;44:2355–61.
36. Persson F, Carlsson L, Duker G, et al., *J Cardiovasc Electrophysiol*, 2005;16:329–41.
37. Goldstein RN, et al., *J Cardiovasc Electrophysiol*, 2004;15:1444–50.
38. Crijns HJ, Van Gelder IC, et al., *Heart Rhythm*, 2006;3:1321–31.