CELL TO BEDSIDE

Ion channel trafficking: A new therapeutic horizon for atrial fibrillation

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Atrial fibrillation (AF) is a common cardiac arrhythmia with potentially life-threatening complications. Drug therapies for treatment of AF that seek long-term maintenance of normal sinus rhythm remain elusive due in large part to proarrhythmic ventricular actions. Kv1.5, which underlies the atrial specific I_{Kur} current, is a major focus of research efforts seeking new therapeutic strategies and targets. Recent work has shown a novel effect of antiarrhythmic drugs where compounds that block Kv1.5 channel current also can alter ion channel trafficking. This work further suggests that the pleiotropic effects of antiarrhythmic drugs may be separable. Although this finding highlights the therapeutic potential for selective manipulation of ion channel surface density, it also reveals an uncertainty regarding the specificity of modulating trafficking pathways without risk of off-target effects. Future studies may show that specific alteration of Kv1.5 trafficking can overcome the proarrhythmic limitations of current pharmacotherapy and provide an effective method for long-term cardioversion in AF.

KEYWORDS Atrial fibrillation; Cardiovascular disease; Cardioversion; Ion channel; Kv1.5; Trafficking

ABBREVIATIONS AF = atrial fibrillation; **ER** = endoplasmic reticulum

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting an estimated 2.2 million adults in the United States.[1] AF is caused by the rapid and irregular activation of the atria by electrical sources outside the normal sinus node. It can be classified as paroxysmal, persistent, or long-standing persistent.[2] The occurrence of AF increases dramatically with age, affecting less than 1% of individuals younger than 50 years to approximately 10% of individuals older than 80 years.[1,3] Importantly, over the past 2 decades, the age standardized death rate (per 100,000 in the United States) has increased from 27.6 to 69.8.[4] Therefore, AF presents a significant increasing health risk with an untold burden for health care costs.

The combination of inefficient atrial contraction and irregular ventricular rate can lead to serious complications. AF-related deaths are due primarily to the increased risk of stroke and heart failure. AF is associated with a nearly fivefold increase in the risk of embolic stroke, with nearly one fourth of all strokes in patients older than 80 years attributable to AF.[5,6] This increased rate of stroke is due to the rapid, uncoordinated atrial rhythm that leads to inefficient contraction of the atria, resulting in pooling of blood in the atria and promotion of thromboemboli formation. The presence or absence of several other risk factors, such as recent cardiac failure, hypertension, age, diabetes, or history of stroke or transient ischemic attack, significantly contributes to the risk of stroke.[7,8] In addition to an increased risk of stroke, atrial thromboemboli can propagate to regions other than the brain, such as the kidneys, mesenteric circulation, or heart itself, where the thromboemboli may induce myocardial infarction. AF also participates reciprocally with several comorbid conditions, including congestive heart failure, thyrotoxic heart disease, and hypertension.[9]

Current therapy for AF is aimed at rate control or rhythm control.[10] In rate control, the goal is to maintain the ventricular rate within a physiologic range by slowing atrioventricular conduction. In rhythm control, the aim of treatment is to restore normal sinus rhythm through pharmacologic cardioversion or through electrical cardioversion or catheter ablation. Catheter ablation is considered second-line treatment of AF, with published success rates of 22% to 85%. Higher success rates are often seen for patients with paroxysmal AF.[2,11–13] Although approximately half of these patients remain asymptomatic, nearly 30% require a second procedure, and 10% to 25% require additional pharmacologic therapy in order to maintain normal sinus rhythm after ablation therapy.[14,15] However, the long-term effectiveness of this technique remains to be fully determined.[9,16]

Pharmacologic cardioversion makes use of antiarrhythmic drugs that target cardiovascular ion channels to achieve normal sinus rhythm control in the treatment of AF.[17–20]

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Pharmacologic cardioversion has an advantage over catheter ablation in that it is not invasive; however, it has been reported to be less effective.[21] If class I or III antiarrhythmic agents are administered within the first 24 hours of AF onset, the reported success rate is 47% to 84%; however, the rate drops sharply for AF that persists longer than 48 hours, achieving cardioversion in only 15% to 30% of patients.[22]

A common negative side effect of antiarrhythmic drug therapy is proarrhythmia in the ventricles due to nonselective ion channel block and/or overlapping expression of ion channels in both the atria and ventricles. More recently, there has been a shift in both academia and industry to target atrial-specific currents in order to terminate AF and maintain normal sinus rhythm while avoiding proarrhythmic risk in the ventricles. One of the main targets in this research effort is the voltage-gated potassium channel Kv1.5, which underlies the I_{Kur} current. Importantly, I_{Kur} is selectively reported in human atria only,[17,20,23,24] where it contributes to repolarization and participates in the control of action potential duration. In human atria, Kv1.5 is a predominant channel mediating repolarization, and alterations in its expression level have been demonstrated in pathophysiologic states such as persistent and paroxysmal AF and chronic pulmonary arterial hypertension.[17,25] More specifically, a marked reduction in Kv1.5 channel protein expression is seen in these pathophysiologic states,[26–28] perhaps as an endogenous compensatory mechanism. Given the atrial-specific expression of Kv1.5 and its known alterations in cardiovascular disease, it is no surprise that development of Kv1.5-specific blockers has been a target of both academic and industrial research efforts for treatment of AF.[29–31] Several compounds have been developed, but these antiarrhythmic drugs have been limited by a lack of channel or tissue selectivity or poor bioavailability. Therefore, there remains an unmet need for the development of safe new compounds with both atrial selectivity and clinical efficacy for long-term treatment of AF.

New therapeutic strategies that focus on regulation of ion channel surface density are emerging from basic research at the bench (Figures 1 and 2).[32,33] Traditional antiarrhythmic drugs target the ion permeability of channels; however, as highlighted earlier, this approach has not yet yielded a satisfactory outcome. I_{Kur} can be decreased in two ways: through a direct effect on conduction properties (classically pore block) of channel subunits or through alterations in surface density of the protein. The steady-state cell surface density of proteins is determined by the balance between anterograde and retrograde trafficking pathways. Anterograde trafficking ensues only after proper synthesis and processing in the endoplasmic reticulum (ER) and Golgi, including quality control mechanisms, glycosylation, and post-translation modification (Figure 1).[34] Retrograde movement initiates with endocytosis, after which internalized proteins can follow multiple routes to different intracellular fates (Figure 1).[35] One well-recognized fate is the targeting of internalized proteins to lysosomes or proteasomes followed by degradation (Figure 1). Alternatively, trafficking through recycling endosomes allows proteins to return to the plasma membrane and protects them from degradation (Figure 1).[36] Sorting at early endosomes to Rab-GTPase specific compartments is now established as an important event determining the intracellular fate of internalized proteins.[37–39] Another important component of the endocytic machinery regulating protein surface levels is the coordinated movement of molecular motors. In general, protein trafficking is highly coordinated between long-range events involving the microtubule-based kinesin and dynein motors and short-range events using unconventional myosin motors.[40–43] A significant and growing body of literature about ion channel trafficking from synthesis to sorting to degradation in multiple tissues and cells systems has been reviewed previously.[44–48] Our discussion centers mainly on recent work focused on acute modulation of ion channel density at the plasma membrane in the heart, where relatively little is known about protein trafficking.

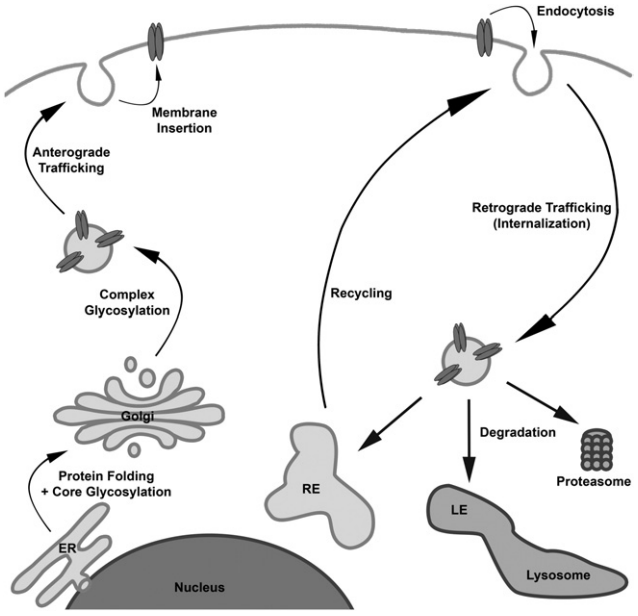

Figure 1 Potential therapeutic intervention points in trafficking of membrane proteins. Each *arrow* represents a regulatory step in the trafficking of membrane proteins that could serve as a potential therapeutic target for modulating steady-state cell surface levels of ion channels. The **left** half of this figure represents an area where much work has been done in the hERG field for treatment of long QT syndrome and other arrhythmias. The **right** half represents an exciting developing field for regulation of Kv1.5 membrane levels in the treatment of atrial fibrillation. ER = endoplasmic reticulum; LE = late endosome; RE = recycling endosome.

Although the precise mechanisms regulating plasma membrane localization and targeting of Kv1.5 in atrial myocytes have not been fully elucidated, several key components and steps are known. Formation of functional Kv1.5 begins in the ER, where tertiary folding is coupled to formation of the quaternary structure through tetramerization of the T1 domain in the amino-terminus of this channel.[49] The first transmembrane segment (S1) of Kv1.5 has also been implicated in the co-assembly of homotetrameric and