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Channeling a New Focus for Heart Failure: Insights into ion channel

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Over 500,000 new patients in the U.S. develop heart failure (HF) annually and sudden cardiac death (SCD) has become a dominant problem in HF management¹. Successful development of pharmacologic therapies that target neurohormonal abnormalities and modulate disease progression has changed the major cause of death in HF patients from progressive pump failure to SCD from cardiac arrhythmias. What underlies the increased risk of SCD in HF patients is only partially understood. While it is clear that underlying scar and fibrosis serve as a powerful arrhythmogenic substrate in patients with ischemic cardiomyopathy, extensive work over the past decade has shown that the failing ventricle undergoes significant electrical remodeling²; that is, the expression of some ion channels increases and expression of others is suppressed. This is of utmost clinical importance, as biophysical studies of many mutant channels responsible for Long QT Syndrome (LQTS) have shown that even subtle alterations in ion channel function can elicit life-threatening arrhythmias.

Electrical remodeling manifests in several ways, but none more prominently than an increase in the electrocardiographic QT interval, a hallmark of abnormally long ventricular repolarization that correlates with the risk of arrhythmias^{3–5}. Repolarization at the level of a myocyte is the sum of multiple and counteracting repolarizing and depolarizing currents during an action potential, each carried by a specific ion channel. A delicate balance between the opposing depolarizing and repolarizing forces underlies normal repolarization and can be adjusted in either direction for specific physiologic purposes by various modulators. As sympathetic stimulation accelerates heart rate, for example, repolarization is enhanced by the actions of the β -adrenergic activated protein kinase A (PKA) on the KCNQ1 K⁺ channel⁶; I_{Ks} activity increases and the action potential duration thus shortens to meet the requirements demanded by the increased heart rate. The heart is not just a bunch of individual cells, however. Proper electrical activity also depends on the efficient and coordinated communication among cells throughout the entire organ, a result of various specialized cell-cell connections.

The delicate balance between repolarization and depolarization that assures proper electrical activity, so essential for physiologic adaptation, can be perturbed with dire consequences. Mutations altering ion channel function or the action of a channel modulator are the root of

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various inherited cardiac arrhythmias such as LQTS, Brugada Syndrome, or catecholaminergic polymorphic ventricular tachycardia. In these cases, abnormal baseline cardiac electrical activity is the substrate for specific triggers that initiate life-threatening arrhythmias. In the failing heart, subject to increased wall stress and neurohormonal feedback attempting to compensate for decreased cardiac output, physiologic signaling mechanisms go awry and change the expression of certain channels or their modulators; the resulting ion channel remodeling is often very similar to what occurs with inherited arrhythmias.

Current pharmacologic treatments designed to address the neurohormonal abnormalities associated with HF do partially correct electrical remodeling and/or prevent the arrhythmogenic triggers, but arrhythmogenic SCD remains a major problem in HF. Thus, implantable cardioverter defibrillators (ICDs), which successfully reduce mortality from SCD in patients with impaired left ventricular function⁷⁻⁹, have become an additional therapeutic option, but the absolute mortality benefit provided by ICDs is relatively small. Clearly, there is a pressing need for new approaches and solutions.

The *Journal of Cardiovascular Pharmacology*, in the accompanying series of review articles, has taken on the challenges of examining where we are and of exploring where we may be going in the quest for new pharmacologic therapies aimed at the treatment of arrhythmogenesis in HF. Opportunities abound for new therapeutic interventions that build upon the growing understanding of ion channels and electrical remodeling during HF by targeting ion channels and their regulatory partners. Starting with an examination of how neurohormonal activation can be a potent and multifaceted ion channel regulator and ending with an in-depth analysis of one drug that holds promise for affecting arrhythmogenesis in HF through targeting a specific ion channel defect, this eight article series succeeds in identifying many of these opportunities and sets the stage for further investigation.

Kurokawa & Abriel begin with a discussion about how activation of the HF-triggered activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic catecholaminergic system modulate ion channel expression through both genomic effects and non-genomic effects. They describe the link between neurohormonal activation—the *sine qua non* of HF and what is now understood to be responsible for many of its adverse consequences—and ion channel dysfunction and remodeling. With this background they address how some current HF therapies, such as aldosterone antagonists, may have direct effects upon arrhythmogenesis¹⁰.

A pair of articles then discusses the role of ion channels and key cytoskeletal elements associated with channels that participate in mechanotransduction, the process by which the forces of cellular strain associated with a hypertrophying and dilating heart are transmitted to the cytoplasm and thereby alter myocyte function. Nilsson & Bennett focus on signaling microdomains and force transduction with a particular emphasis on ankyrins. These scaffolding proteins serve as critical spatial organizers for a variety of ion channels and transporters and ankyrin dysfunction has been found to underlie human disease¹¹. Stiber *et al.* review mechanosensitive (stretch-activated) channels, which are instrumental in transducing the aberrant cellular forces associated with HF into cellular signaling pathways. With a particular spotlight on TRPC channels, they discuss the possibilities of stretch-activated channels as therapeutic targets in HF.

The next two articles address the role of ion channel regulators. Bers & Grandi summarize the modulatory effects of Ca^{2+} /calmodulin-dependent kinase II (CaMKII) on cardiac ion channels function, discussing CaMKII actions upon the sarcolemmal L-type Ca^{2+} channel, the sarcoplasmic reticulum ryanodine receptor, the cardiac Na^{+} channel $\text{Na}_v1.5$, and the pore-forming subunit for the transient outward K^{+} channel, I_{to} . With so many targets crucial to the cardiac action potential, this review helps elucidate a spate of recent reports from several groups

showing that CaMKII activity promotes maladaptive responses in HF¹². Gonazalez *et al.* describe new developments in the understanding of post-translational protein modification by nitrosylation and its consequent regulatory functions, with a specific emphasis on components of the excitation-contraction machinery. The recent discovery that a scaffold for nitric oxide synthase (NOS, the enzyme that generates the NO behind nitrosylation), syntrophin, is a Long QT Syndrome locus¹³ shows that nitrosylation may be a key regulator of arrhythmogenesis and is especially relevant since nitric oxide synthase activity is affected by HF.

The series then turns to gap junctions in an article by Hesketh *et al.* These cell-cell communication channels, which allow coordinated, rapid communication and the fast spread of electrical activity among cardiac myocytes, may be new therapeutic targets given that dynamic altered gap junction function and expression are associated with arrhythmogenesis.

The final two manuscripts get to the heart of the matter at hand by focusing on specific therapies for HF that target cardiovascular ion channels. Doshi & Marx provide an overview of recently described or proposed treatments that target a variety of channels, transporters, and pumps. Ranolazine, a blocker of the late Na⁺ current that may be arrhythmogenic in HF, is the subject of the review by Maier. Both of these reviews balance discussions of the pharmacology and physiology in the context of data from recent clinical trials.

It has been a pleasure and an honor to serve as the guest editor for this review series. I wish to express my gratitude first to the authors of these interesting manuscripts and then to the dedicated and expert group of outside reviewers for their helpful comments and insight. I believe the authors of the collected reviews would echo my sentiments that I sincerely hope and anticipate that this series serves as an educational boost for promoting further efforts into the development and treatment of SCD.

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