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Kir2.1 & Nav1.5 in sickness and in health: Who needs a chaperone when they have an alpha partner?

Benjamin Strauss, BEng and **Fadi G. Akar, PhD, FHRS**

Cardiovascular Research Center, Icahn School of Medicine at Mount Sinai, New York, NY

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The ventricular action potential is sculpted by the orchestrated activity of multiple depolarizing and repolarizing ion currents, exchangers, and pumps. Owing to the time and voltage dependency of these ion transport mechanisms, even a subtle change in one will influence the activity of the others. This, in turn, will profoundly impact the electrophysiological properties of the myocyte and the heart as a whole. Indeed, altered ion channel activity in response to pharmacological agents, acquired diseases, or congenital disorders is a major cause of malignant ventricular arrhythmias leading to sudden cardiac death.[1]

Chief among the many cardiac ion currents that generate the action potential are the inward rectifier K current (I_{K1}) and the voltage-gated fast inward Na current (I_{Na}), along with their pore-forming alpha subunits, Kir2.1 and Nav1.5.[2] The relative importance of these two channels is underscored by the tight control that they exert on myocyte excitability. While I_{K1} establishes the resting membrane potential, I_{Na} is responsible for generating the action potential upstroke (or phase 0). Since the driving force for I_{Na} is fueled by the difference in voltage between the resting membrane potential and the reversal potential for Na, I_{K1} exerts primary control over myocyte excitability and secondary control over action potential formation and propagation. The relevance of the functional interplay between I_{K1} and I_{Na} extends beyond the regulation of normal excitability as it plays a particularly important role in pathophysiological situations, such as hyperkalemia and ischemia. In both settings, membrane depolarization reduces the driving force for I_{Na} and promotes its partial inactivation.

In addition to the indirect influence of I_{K1} on I_{Na} that is mediated by its voltage dependence, accumulating evidence in the literature over the past few years is highlighting the importance of direct molecular interactions between the major subunits that form these channels. Specifically, an increase in the expression of Nav1.5 at the cell membrane has

Address correspondence to:**Fadi G. Akar, PhD, FHRS**, Associate Professor of Medicine, Cardiovascular Research Center, Icahn School of Medicine at Mount Sinai, New York, New York 10029, Tel: 212-824-8920, Fax: 212-241-4080, fadi.akar@mssm.edu, URL: http://labs.icahn.mssm.edu/akarlab/.

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been shown to result in a corresponding increase in Kir2.1 channels and vice versa.[34] This curious interplay in channel expression has given rise to the so-called principal of reciprocal modulation of I_{K1} and I_{Na}. The dynamic reciprocity in current function is likely to have profound consequences not only to cardiac excitability under normal physiological conditions, but also for the pathogenesis and maintenance of complex ventricular arrhythmias, since the balance between I_{K1} and I_{Na} is a key determinant of the frequency and stability of fibrillatory rotors.[5]

Kir2.1 and Nav1.5: For better or for worse

What causes the mutual reciprocity in the activity of these two seemingly distinct depolarizing and repolarizing ion fluxes? As it turns out, the answer to this basic question is anything but trivial. This is because the activity of any given ion channel depends not only on its pore-forming alpha subunit, but rather on a myriad of auxiliary, anchoring and adapter proteins that form large multi-protein macromolecular complexes. Furthermore, the individual components of these ion channel complexes undergo intricate regulation by diverse cell signaling cascades and are subject to a host of post-translational modifications that alter their function. Adding to this multi-tiered levels of complexity is the fact that ion channel regulation commences at the time of transcription of the channel subunits, and continues through their translation, sorting, forward trafficking, membrane targeting, insertion, recycling, and degradation.[6] In that regard, determining the exact nature of the molecular interactions that mediate the dynamic reciprocity of two major cardiac ion channels requires nothing short of a herculean effort.

Fortunately, diligent work by thought leaders in the field, including an elegant study in this issue of *Circulation Research*[7] is shedding major light on this important and understudied area. The steady work of these investigators is systematically revealing both the nature and implications of the physical interactions between Kir2.1, Nav1.5 and a growing list of other members of their channelosome.[2, 3, 8] Despite knowledge of the dynamic reciprocity of Kir2.1 and Nav1.5 as revealed by their ability to control each other's cell surface expression, major questions remain. For example, at what point during the life cycle of these two critical proteins do they associate with one another? Are they processed separately and do they undergo distinct trafficking pathways as they journey to their ultimate destination within specific microdomains of the cell membrane such as its lateral border, intercalated disc or transverse tubules? Do these channels share separate or common trafficking partners? Do they "casually" meet one another and initiate their physical/functional interactions after or before they are embedded in the membrane? Does their shared destiny manifest at a much earlier stage in their life cycle? And if so, does this subject those life partners to mutual regulation and condemn them to mutual annihilation?

In this issue of the *Circulation Research*, [7] the Jalife group addresses many of these fundamental questions using a rigorous, multi-disciplinary approach that leaves no stone unturned. The study convincingly demonstrates that Nav1.5 channels traffic more efficiently when they are joined by Kir2.1 compared to when they are separated from their K channel partner. This highlights the importance of the native association between the two alpha subunits well before they reach their intended destination to form functional currents.

Furthermore, using trafficking deficient mutant Kir2.1 channels that cause Andersen-Tawil Syndrome, these authors document the mutual impairment in the forward trafficking of wild type Nav1.5 channels without a change in its total cellular protein content or its gating properties.[7] They go on to demonstrate that the tight association of these two alpha subunits occurs at a very early time point in their biosynthetic pathway. They highlight the role of adaptor protein complex 1 which was previously shown to incorporate Kir2.1 channels into clathirin coated vesicles in the export of Nav1.5 at the level of the trans-Golgi.[9]

Looking ahead

The paradigm shifting work by the team of investigators from Michigan and Madrid published in this issue of *Circulation Research*[7] raises multiple intriguing questions that will require active investigation in future studies. For example, the downside of the mutual demise of Kir2.1 and Nav1.5 channels when only the former is rendered trafficking deficient is obvious. But surely there must be an upside to this elaborate, self-destructive scheme that attempts to shut down excitability in the face of a severe K channel mutation. After all, even a classic Na channel chaperone (β2) that harbors a mutation associated with Brugada Syndrome will happily traffic solo to the cell membrane leaving its pore forming Nav1.5 partner behind.[10] A key question to be addressed in future studies is whether pharmacological or gene based[11] strategies used to rescue defective trafficking of Kir2.1 or Nav1.5 channels alone could be tailored for the re-trafficking of the combined channelosome.

The tight molecular association between the two alpha subunits that is documented in this study suggests presence of substantial phenotypic overlap between the Andersen-Tawil syndrome arising from trafficking deficient Kir2.1 and Na channelopathies, such as the Brugada Syndrome. Of note, some Andersen-Tawil causing mutations in Kir2.1 result in a mixed phenotype that gives rise to an arrhythmic disorder resembling catecholaminergic polymorphic ventricular tachycardia. [12, 13] Finally, the present findings have major implications for arrhythmias in other heritable disorders such as Arrhythmogenic Cardiomyopathy. Although classically considered to be a disease of the desmosome, mutations in intercalated disc proteins can lead to the mutual dysregulation of both Nav1.5 and Kir2.1 via common partners, such as SAP97.[14, 15]

In summary, the present findings by Ponce-Balbuena et al[7] offer a humbling perspective on the complexity of ion channel interactions in both health and disease. The study is expected to impact the arrhythmia field for many years to come as we re-consider insights garnered solely from the reductionist approaches that are typically used to study mutations in individual ion channel proteins.

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