Despite major breakthroughs in cardiovascular diagnostics and therapies over the past century, diseases of the heart remain a leading cause of death in the United States, nearing 600,000 deaths per year. Most of these deaths (200,000–400,000 per year) are due to cardiac arrhythmia in which syncope and sudden death are often the first manifestations of heart disease. Foundational work by Wang et al in the mid-1990s cemented the critical role of ion channel dysfunction in human arrhythmia. Today, we know that ≈35% of sudden unexplained death and ≈20% of sudden infant death syndrome cases may be explained by mutations in cardiac ion channels (cardiac channelopathies). Furthermore, defects in ion channel function have widely been observed in common forms of heart failure. This year marks the 25th anniversary of publication of the preliminary Cardiac Arrhythmia Suppression Trial (CAST) findings in the New England Journal of Medicine. Here, we discuss new findings reported by Shy et al on Na Channel macromolecular complexes reported in this issue of Circulation and reflect on lessons learned in the ensuing years after CAST that may help propel advances in treatment of cardiovascular disease over the next quarter-century.

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Defects in voltage-gated sodium (Na) channels are among the best characterized of the cardiac channelopathies. Na channel complexes are composed of a large ≈260-kDa pore-forming α-subunit and an associated auxiliary β-subunit. In humans, Na α-subunits are encoded by 9 genes, whereas 4 genes encode Na β-subunits. Beyond heart, Na channel gene defects are linked to a host of excitable cell phenotypes, including epilepsy and seizures, myotonia, and erythromelalgia. Although multiple Na channel α-subunits are expressed in heart, Na 1.5 (SCN5A) is the primary α-subunit responsible for conducting inward sodium current (I\text{Na}) at the outset of the action potential (phase 0). Human SCN5A gene defects leading to alterations in Na 1.5-dependent I\text{Na} are now linked to many cardiac arrhythmia phenotypes, including sick sinus syndrome, atrial fibrillation, progressive and nonprogressive heart block, type 3 long-QT syndrome, and Brugada syndrome.

The Na 1.5 channel protein consists of 4 membrane domains (DI–DIV), with each domain made up of 7 transmembrane spanning helices (S1–S6; Figure). Each membrane-embedded helix serves specific roles to regulate Na+ flux through the channel. For example, S5/S6 helices form the Na+ conductance pore, whereas the S4 helix serves as a voltage sensor to facilitate channel activation. Cytoplasmic loops connect DI through DIV, with additional intracellular domains at both the N- and C-termini of the protein (Figure). To date, the majority of arrhythmia variants are located in regions of the SCN5A gene that affect channel biophysical properties. However, advances in genetics, small-animal physiology, signaling, and molecular biology over the past decade have powered new studies highlighting the role of Na 1.5-associated proteins in the regulation of I\text{Na}, as well as dysfunction in heart failure and arrhythmia. In fact, these findings are not limited to Na 1.5 but have been illustrated for voltage-gated potassium and calcium channels, as well as membrane transporters and non–voltage-gated channels.

Targeting Na 1.5 to prevent arrhythmias has a troubled history, exemplified by CAST in which the Na+ channel–blocking agents encainide and flecainide increased mortality compared with placebo in patients after myocardial infarction. Despite the fact that 25 years have passed since this landmark report, the field struggles to move beyond lessons learned about the proarrhythmic potential of antiarrhythmia drugs. The study from Shy and colleagues in this issue of Circulation may suggest a way forward by adding to mounting evidence that multiple Na 1.5 populations exist within the cardiomyocyte. These populations differ not only by location (eg, intercalated disk, transverse tubule, lateral membrane) but also by the nature of their interacting partners, regulation, and likely drug sensitivity. In fact, multiple Na 1.5 macromolecular complexes form as a result of a large number of interactions between Na 1.5 and accessory, adapter, cytoskeletal, and regulatory proteins (Figure). Importantly, Na 1.5 interacts with different partners, depending on its location in the cell. Functionally, this contributes to a heterogeneous population of Na 1.5 within the cell. At the intercalated disk where cells are electrically and mechanically coupled, the Na 1.5 macromolecular complex includes the adapter protein ankyrin-G, as well as calcium/calmodulin-dependent protein kinase II (CaMKII) via interaction with β2-spectrin. Na 1.5 is also found at transverse tubules, together with ankyrin-G. In fact, SCN5A mutations that block ankyrin-G binding alter Na 1.5 membrane trafficking and are associated with Brugada syndrome. Other studies have identified possibly a second population of channels at the intercalated disk that interact with the adapter protein synapse-associated protein 97 (SAP97) via a PDZ-domain (named for its presence in the postsynaptic density protein complex). The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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PSD95, the disk large tumor suppressor Dlg1, and zonula occludens-1 (ZO1)–binding motif in the Na\textsubscript{v}1.5 C terminus. Potential interaction between Na\textsubscript{v}1.5 and both connexin43 and plakophilin-2 at the intercalated disk has also been reported. At the lateral membrane, recent work by Petitprez and colleagues\textsuperscript{15} has identified an important role for the syntrophin/dystrophin complex in targeting Na\textsubscript{v}1.5.

The study from Shy and colleagues\textsuperscript{8} in this issue of Circulation provides important new in vivo data on the characteristics of distinct Na\textsubscript{v}1.5 complexes at the intercalated disk and lateral membrane, highlighting the structural and functional differences between at least 2 of the potential Na\textsubscript{v}1.5 populations. On the basis of the previously observed interaction of Na\textsubscript{v}1.5 with PDZ domain–bearing proteins at both the lateral membrane (syntrophin) and intercalated disk (SAP97), the authors developed a knock-in mouse that expresses Na\textsubscript{v}1.5 lacking the PDZ domain-binding motif (ASIV). The authors report a significant decrease in Na\textsuperscript{+} current in ventricular myocytes from the ASIV mice compared with wild-type mice, coupled with a loss of Na\textsubscript{v}1.5 at the lateral membrane,\textsuperscript{8} consistent with previous reports. Notably, Na\textsubscript{v}1.5 at the intercalated disk was unaffected in ASIV myocytes, an unexpected finding given that prior studies in myocytes with acute knockdown of SAP97 expression showed disrupted Na\textsubscript{v}1.5 intercalated disk targeting.\textsuperscript{15,17} These new in vivo data strongly support a PDZ-domain–dependent interaction for lateral membrane Na\textsubscript{v}1.5. Conversely, these in vivo findings clearly demonstrate that Na\textsubscript{v}1.5 is targeted to the intercalated disk independently of the PDZ-domain protein association. Finally, the authors report a de novo human arrhythmia mutation in the Na\textsubscript{v}1.5 PDZ-domain–binding motif that negatively affects partner interaction and Na\textsuperscript{+} channel function, suggesting a role for this channel population in human cardiovascular disease.

In light of growing evidence that multiple Na\textsubscript{v} channel complexes exist in the myocyte, can we exploit the unique characteristics of these distinct populations for therapeutic advantage? Currently, Na\textsuperscript{+} channel–blocking drugs that target the late (persistent) phase of Na\textsuperscript{+} current (as opposed to the rapid component) are gaining favor as potential agents to treat cardiovascular disease/arrhythmias.\textsuperscript{15} For example, the antiangiinal Na\textsuperscript{+} channel blocker ranolazine with unique kinetics that preferentially target the late Na\textsuperscript{+} current has proven effective in preventing arrhythmias and improving outcomes in a number of animal models and is in limited clinical trials for heart failure.\textsuperscript{14} Going forward, can we apply these findings to devise new antiarrhythmia strategies based on the distinct profile of a specific Na\textsuperscript{+} channel population? In other words, are there unexplored avenues for preventing arrhythmias/disease by targeting specific Na\textsuperscript{+} channel complexes? To answer this question, it is important to consider the cellular factors that regulate the cardiac Na\textsubscript{v}1.5 late current. Mounting evidence supports a central role for the multifunctional serine/threonine CaMKII in controlling the magnitude of the late current through direct phosphorylation of the Na\textsuperscript{+} channel.\textsuperscript{15,20} CaMKII is preferentially targeted to Na\textsubscript{v}1.5 at the intercalated disk via direct interaction with the actin-associated cytoskeletal protein \(\beta\)\textsubscript{c}–spectrin. Furthermore, targeted disruption of the spectrin/CaMKII interaction decreases late Na\textsuperscript{+} current without affecting the peak. Together with the new data from Shy and colleagues\textsuperscript{8} and prior functional work by Lin et al,\textsuperscript{12} these findings suggest that perhaps by targeting intercalated disk Na\textsubscript{v}1.5 (eg, altering spectrin levels/interaction with CaMKII) we can preferentially target the proarrhythmic component of the Na\textsuperscript{+} current while protecting/maintaining key populations of Na\textsubscript{v}1.5 required for cardiac conduction.

As the 25th anniversary of the CAST publication comes and goes, it is appropriate to reflect on the importance of this work and the many ways it has affected basic and translational cardiac arrhythmia research. At the same time, it is important to recognize the sea change that has transpired in our understanding of Na\textsuperscript{+} channel biology and our ability to manipulate channel function. It is our expectation that major therapeutic advances will be made over the next 25 years by focusing on specific Na\textsuperscript{+} channel macromolecular complexes to fine-tune Na\textsuperscript{+} function.

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Disclosures

None.

References


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