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INVITED EDITORIAL

The Role of Nav1.8 in Cardiac Electrophysiology—a Matter of the Heart or the Nerve?

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SCN5A/Nav1.5 is the canonical voltage-gated cardiac sodium channel conducting depolarizing I_{Na} current in the heart. Moreover, *SCN5A*/Nav1.5 channels harboring gain-of-function mutations with impaired inactivation or pathologically over expressed/over activated *SCN5A*/Nav1.5 channels conduct pathological late $I_{Na,L}$, which impairs repolarization in the heart—relevant in a variety of different cardiac arrhythmogenic diseases such as long QT syndrome, heart failure, and cardiac hypertrophy (1–3). *SCN10A*/Nav1.8, in contrast, is an important voltage-gated sodium channel conducting depolarizing I_{Na} current in the nervous system—particularly in dorsal root ganglia, nociceptive nerves, and cardiac nerves/ganglionated plexi (4–6).

This classical distinction between cardiac and neuronal sodium channel isoforms, however, has been challenged in recent years: the potential role for the neuronal *SCN10A*/Nav1.8 in modulating cardiac electrophysiology in health and disease and its potential impact on arrhythmia susceptibility is an ongoing matter of debate. Genome-wide association studies have associated variants in *SCN10A*/Nav1.8 with alterations of cardiac conduction (7, 8) and with atrial fibrillation (9, 10). *SCN10A*/Nav1.8 mutations have been identified in Brugada syndrome (11, 12). Moreover, recently, it has been demonstrated that *SCN10A*/Nav1.8 is upregulated in heart failure (13) and cardiac hypertrophy (14), thus contributing to electrical remodeling in diseased hearts. All these studies suggest that *SCN10A*/Nav1.8 may play a role in arrhythmogenic cardiac diseases.

But is the channel expressed in the heart or rather in cardiac neurons? And is it thus exerting direct effects on cardiac electrophysiology or are its effects mediated via the nervous system?

In their study in this issue, Casini, Remme, and colleagues aimed at elucidating whether *SCN10A*/Nav1.8 is expressed and functionally active in the healthy heart (15). In a thorough approach, they investigated the functional relevance of *SCN10A*/Nav1.8 in different types of cardiomyocytes (CMs) (e.g., atrial and ventricular CMs), and in different species (e.g., rabbit left ventricular CMs, human left atrial CMs, and human-induced pluripotent stem cells derived cardiomyocytes (hiPSC-CMs))—focusing on the contribution of Nav1.8 to both peak and late sodium current under normal, physiological conditions. In cardiomyocytes from all different species investigated, resting membrane potentials, action potential (AP) amplitudes, and AP upstroke velocities were all unaffected by the Nav1.8-blocker A-803467 and Nav1.8-based late sodium current was undetectable. Similarly, Nav1.8-blockade had no effect on APD in human atrial cells—while a slight shortening of APD was observed in rabbit CMs and hiPSC-CMs; likely due to some time-dependent run-down in the latter cells. All these patch clamp findings indicate no (relevant) functional role of Nav1.8 in the healthy myocardium. To complement their functional assessment, the authors investigated cardiac mRNA expression levels of *SCN10A*, which were found to be low to absent in human atrial tissue, rabbit ventricular tissue, and hiPSC-CMs, further supporting the notion that *SCN10A*/Nav1.8 might not be important for the physiological electrical function in the healthy heart.

Important to note, to verify their findings and conclusions, the authors have performed several additional studies investigating the validity of the employed methods (15). To check whether run-down may underlie (in part) the apparent minor effects of the Nav1.8-blocker on APD in some of their experiments and the fact that these effects were not reversible upon washout, the authors have included vehicle time-matched control measurements. These controls clearly demonstrate shortening of APD over time—similar as observed in the presence of

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the Nav1.8-blocker, supporting the notion that the observed apparent small shortening of APD induced by A-803467 in rabbit CMs is likely a time-dependent effect independent of the blocker. These experiments clearly highlight the importance of running time-matched controls. Moreover, to verify that Nav1.8-blocker A-803467 is indeed working on Nav1.8-mediated sodium current, the authors have additionally recorded action potentials (APs) from murine intracardiac neurons in the presence and absence of Nav1.8-blocker A-803467, demonstrating its general functionality on neuronal I_{Na}: in the presence of A-803467, AP upstroke velocity was reduced, an effect that was reversible upon washout (5, 15).

Transcription of *SCN10A* was first investigated in human iPSC-CMs and human left atrial tissue and compared with *SCN5A* mRNA levels in the same samples. The authors have then elegantly complemented these data with *SCN5A* and *SCN10A mRNA* expression data in other cardiac tissues (rabbit left ventricle, hiPSC-CMs, and human right and left atria), which they have extrapolated from analyses of online RNA sequencing raw datasets previously published, providing a nice example of how published raw data can be reused for different research questions.

Support for the observation by Casini and colleagues of a virtually absent expression of *SCN10A* in healthy rabbit, mouse, and human cardiomyocytes (15) has recently been published by Gando et al. (16). In this study, no Nav1.8 protein or mRNA expression was detected in the specialized cardiac conduction system of mice, and rat and human ventricles—even in subjects with sudden unexplained death and pathogenic *SCN10A* mutations, suggesting that the effect of *SCN10A*/Nav1.8 on cardiac electrical function is likely to be extra-cardiac in origin.

One prime candidate is the nervous system; and indeed, several studies have investigated and verified an effect of Nav1.8-blockade in cardiac ganglionated plexi/intracardiac neurons on cardiac electrophysiology, cardiac conduction, and AF inducibility (5, 6, 17). Another mechanism by which *SCN10A* may impact on cardiac electrophysiology—f. ex. in Brugada syndrome—is via a genetic interaction with *SCN5A* (via enhancer-promotor interactions between *SCN10A* and *SCN5A* loci) (18).

In contrast to these findings in healthy, structurally normal hearts and cardiomyocytes, in disease states—such as heart failure and cardiac hypertrophy—a significant and relevant upregulation of *SCN10A*/Nav1.8 mRNA and protein expression has been observed both in cardiac tissue and in cardiomyocytes and its functional relevance has been verified by blocking experiments (13, 14), suggesting that in the diseased, remodeled heart, the neural form Nav1.8 may indeed directly affect the cardiomyocyte's electrical function.

The role of *SCN10A*/Nav1.8 in cardiac electrical function is thus not a matter of the heart or the nerve but rather of both—depending on the heart's state.

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