Editorial

Cardiac sodium channels: Dysregulation meets myocardial failure

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See article by Hesse et al. [12] (pages 498–509) in this issue.

Within the orchestra of cardiac ion channels, voltage–gated Na⁺ channels have a key function in the determination of the amplitude and slope of the action potential upstroke. Both are important in the control of impulse conduction velocity and maintenance of appropriate waves of excitation through the working myocardium. The main (α-) subunit of the cardiac sodium channel is encoded by the SCN5A (Nav1.5) gene, and the INa current mediated is responsible for the membrane depolarization. Fast inactivation of sodium channels appears within milliseconds, and the vast majority of sodium channels transit from the open state to a non-conductive state. Gating dysfunction or changes in the number of functional channels of cardiac sodium channels are linked to several cardiac arrhythmias [1–4]. Meanwhile, more than 170 different SCN5A mutations have been reported (currently, 77 for LQT-3, 90 for Brugada syndrome, 10 for conduction disease; see http://www.fsm.it/cardmoc/), and this has enabled evaluation of structure-function relationships of the sodium channel.

Analysis of several of these mutations has consistently demonstrated that loss of function is the basic mechanism in Brugada syndrome or conduction disease, which is related to multiple mechanisms that include failure of sodium channel protein expression and, importantly, changes in the voltage- and time-dependent channel kinetics. The observation that the majority of ion and, in particular, sodium channel mutations occur in patients with structurally normal hearts led to an initial concept of ion channel disorders as “primary electrical heart disease” arising in myocardium that is otherwise structurally and functionally normal. However, this concept has been challenged by the observation of families with a Brugada-like ECG but having dilated (right ventricular) cardiomyopathy [5] and also by histopathologic reports from biopsies of Brugada syndrome patients with or without evident sodium channel mutation that had inflammatory changes, even when comprehensive clinical assessment was unremarkable [6]. These observations may suggest that the Brugada syndrome ECG pattern is not as specific as anticipated and may reflect a more common electrical manifestation of structural abnormalities in the right ventricle with a different background.

The complexity of sodium channel-related clinical phenotypes further enforced investigations to define the regulatory elements of sodium channel gene expression including identification of promoter and transcription initiation sites upstream of human SCN5A. Moreover, the haplotype structure and sequence of the SCN5A promoter has been defined [7], and transcriptional regulation and sodium channel function is under control of many factors [8], including splice variants, other β-subunits, phosphorylation, calmodulin, ankryns, tyrosine kinases or phosphatases, and C-terminally located domains for NEDD4-related ubiquitination or syntrophin proteins.

In addition to genetically determined arrhythmia syndromes, a heterozygous SCN5A missense mutation (D1275N) was first associated with autosomal dominant dilated cardiomyopathy (DCM) and conduction disease (CDM1E)[9]. The specific mechanism of sodium channel disturbance is not yet
known. Another report supported a putative role of cardiac sodium channel dysfunction for familial heart failure and ‘rhythm disturbances’ [10], since the SCN5A gene was within the candidate region of previous linkage data. A total of four specific heterozygous missense mutations (D1275N, T220I, R814W, D1595H) and one insertion mutation (2550-2551insTG) in SCN5A were meanwhile reported from patients with a CDM1E phenotype. A key question is whether these different phenotypic consequences of sodium channel dysfunction result from INa alteration alone or on-top disturbances of channel regulation and interaction with structural proteins, e.g., syntrophins [11].

In this issue of Cardiovascular Research, Hesse et al. reported on ectopic expression of the zinc finger protein Snail in transgenic (TG) mice that resulted in a progressive, typical DCM phenotype together with conduction disturbances and sodium channel down-regulation [12]. The Snail family of zinc finger proteins are transcriptional repressors that regulate genes associated with cell-cell adhesion. In mice, Snail expression is usually present in the embryonic murine heart during early (intrauterine) development. When expressed post natum, Snail TG+/TG- mice were viable, whereas TG+/TG+ mice were lethal. Also, ECG recordings showed typical findings for DCM with an atrioventricular conduction disturbance, i.e., prolonged PR interval and QRS widening, all in the absence of changes in connexin 43 and 45 expression. Interestingly, isolated myocytes from TG+ mice had a reduced upstroke rate of the action potential and, consistently, a strong reduction in sodium current (INa) amplitude together with a reduced gene expression. The authors further elegantly showed that, indeed, the Snail repressor domain is capable of controlling SCN5A promoter activity and that inhibition of E-box motifs in the SCN5A promoter region impaired Snail binding. Taken together, Snail TG+ mice showed typical DCM and myocytes had reduced INa through Snail-mediated SCN5A down-regulation.

Obviously, non-SCN5A related pathways under control of Snail cannot be excluded to contribute to the DCM phenotype, but, together with the data from DCM families with SCN5A mutations, an intriguing link appears likely. Of note, in the infarcted and failing heart, alterations in sodium channel gene expression take place, and in the mouse heart, several brain-type sodium channels (localized at the z-lines within the t-tubular system) contribute significantly to depressed myocardial contractility when selectively blocked by TTX. Is fibrosis of the conduction system first and myocardial contractility second in Snail TG+ mice? Can Snail be reprogrammed after birth, e.g., in heart failure? Is genetically determined DCM from SCN5A mutations linked to Snail pathways and/or alterations in the cytoskeleton? These are challenging questions that will further give important insights about the probably underestimated link between the cardiac sodium channels and contractile function of the myocardium.

References