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Review article

The promiscuous nature of the cardiac sodium current

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Abstract

Voltage-gated sodium channels (Na_Vs) are essential in propagating neuronal electrical impulse and triggering muscle contraction. In the heart, the Na^+ channel isoform $Na_V1.5$ is strongly expressed and in the past was thought to be solely responsible for generating the cardiac Na^+ current (I_{Na}). Recent studies, however, revealed that neuronal and skeletal muscle Na^+ channel isoforms are also expressed in the heart and contribute to cardiac I_{Na}. Amongst the findings is that many neuronal type Na_Vs are expressed in specific areas of the conduction system and ventricles. The contribution of these TTX-sensitive channels to normal cardiac function remains unclear but these data raise the possibility of a more prominent role of TTX-sensitive channels in conduction. Moreover, cardiac arrhythmias are commonly observed in many neuronal and musculoskeletal diseases despite their exclusive linkage to mutations in the neuronal and skeletal muscle sodium channel isoforms. The cause for these arrhythmias remains poorly understood. These recent findings indicate that neuronal and skeletal muscle sodium channels are expressed in areas of the heart that may be involved in the clinical phenotypes observed. The purpose of this review is to give an overview of the evidence for the presence of TTX-sensitive Na_V isoforms in the heart and present the hypothesis brought forward so far for their direct role in cardiac function. These data demonstrate the promiscuous nature of the cardiac sodium current at the molecular level and should help us to bridge the gap that exists between our understanding of cardiac physiology and arrhythmias associated to brain and myotonic diseases.

Keywords: Sodium channels; Arrhythmias; Cardiac; Neuronal; Skeletal; Myotonia

Contents

1. Introduction

The initial linkage of idiopathic forms of long QT syndrome (LQTS) to inherited mutations in genes *KCNQ1*, *KCNH2* and

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SCN5A, respectively coding for the α-subunit of the ion channels responsible for the slow and rapid components of the cardiac repolarizing current I_K and the fast cardiac sodium current I_{Na} [1–3] laid the basis for the study of pathologies linked to naturally occurring ion channel defects, commonly referred to as channelopathies.

Over the last decade, sodium channelopathies have emerged as a major cause of cardiac arrhythmias, such as long QT syndrome [4–6], Brugada syndrome [7–10], and conduction disease [11,12], and *were* related to cases of sudden infant death [13–15]. An increased contribution of late sodium current [4–6] to phase 2 repolarization, preferentially in mid-myocardial cells [16], was found to be responsible for the QT prolongation in LQTS. The arrhythmogenic substrate in Brugada syndrome was linked to a decreased contribution of sodium current and premature repolarization of the right ventricle epicardium [8,17]. These studies clearly demonstrate the important contribution of the sodium current to cardiac repolarization and the arrhythmogenic substrate generated by modulation of *SCN5A* expression.

Recent evidence, however, show that *SCN5A* is not expressed in all cardiac tissues and indicate that TTX-sensitive sodium channels (TNa_V), abundant in neuronal and skeletal muscle tissues, not only contribute to the heart ventricular function but are also dominant in some areas of the conduction pathway. This raises the possibility that TNa_Vs expressed in the heart contribute to arrhythmias related to musculoskeletal and neuronal diseases. The purpose of this review is to summarize our current knowledge on the distribution of TTX-sensitive sodium channels within the heart and highlight their contribution to normal cardiac function and their potential involvement in arrhythmias linked to neuronal and myotonic Na^+-channelopathies.

1.1. Historical perspective

Coordinated contraction of the heart ventricles is triggered by a spontaneous wave of electricity termed action potential (AP) that arises from sino-atrial node (SAN) cells located in the atrium near the coronary sinus. From the SAN, the AP spreads rapidly through the right and left atrium and converges towards the atrioventricular node (AVN). In AVN, the AP is slowed and directed towards specialized bundles of conducting fibers divided into two branches, the right and left HIS bundles. At the end of the HIS bundles, small nerve-like Purkinje fibers (PF) spread the electrical impulse throughout the ventricles (V) and trigger contraction [18]. This particular junction between PF and ventricular cells is of crucial importance for triggering contraction of the ventricles.

The characteristics of the AP and its duration vary along the conduction pathway and in the ventricles. In the SA and AV nodes, calcium currents are primarily responsible for the initial systolic depolarization of the AP. In the atria, PF and ventricles, however, the activation of voltage-dependent Na^+ currents generates a more rapid AP upstroke. This high degree of cardiac electrical specialization is beautifully reflected by the impressive variety of potassium channel genes expressed in each anatomical constituent of the heart tissues. In sharp contrast, however, only one type of sodium channel (Na_V) was widely believed to be electrically active in cardiac tissues until a few years ago, despite earlier evidence suggesting the presence of channels with high and low affinities for the specific Na^+ channel blocker tetrodotoxin [19,20].

The primary difficulty in trying to electrically dissect the contribution of different Na_V isoforms comes from their very similar current kinetics. Because of the rapid gating of voltage-dependent sodium current one has to perform experiments at room temperature to slow its kinetics and reduce its amplitude to levels that insure control of the myocyte membrane potential during its recording. Since TNa_Vs contribute to a small fraction of the total sodium current in physiological conditions, such experimental settings further mask their contribution to the cardiac sodium current. Small structural differences between cardiac and neuronal sodium channels nonetheless create pharmacological and gating signatures that can be used for their identification.

At the molecular level, voltage-dependent Na^+ channels are composed of a pore-forming α-subunit that consists of four domains each containing six transmembrane segments [21–24] and, accessory β-subunits [25,26] that modulate the gating, pharmacological properties and amplitude of the electrical current. The Na^+ channel α-subunit $Na_V1.5$, encoded by the *SCN5A* gene, determines the major electrophysiological and pharmacological properties of I_{Na} in ventricular cardiomyocytes in normal conditions [21,27]. $Na_V1.5$ and the TNa_V isoforms differ in their respective voltage-dependent gating and affinity for local anaesthetics such as lidocaine, commonly used as antiarrhythmic agents [28–30]. This cardiac-specific isoform is also relatively resistant to the alkaloid neurotoxins tetrodotoxin (TTX) and saxitoxin (STX) while the skeletal muscle ($Na_V1.4$) and neuronal subtypes ($Na_V1.1$–1.3, $Na_V1.6$–1.7) have a 100-fold higher affinity for TTX and STX [31]. These properties were initially used to assess the contribution of the TTX-sensitive and TTX-resistant sodium currents to the different phases of the cardiac action potential and indirectly provided the first evidence for at least two sodium channel isoforms in heart tissues.

In 1979, Coraboeuf et al. [19] showed that relatively low TTX concentrations could shorten the action potential of PF and slow their automatic beating rate. The effects on AP duration and rhythm were attributed to the gating properties of $Na_V1.5$, namely the presence of a late (sustained) inward current more sensitive to TTX [32,33] and a window current generated by the overlap between the steady state activation and inactivation curves over a restricted voltage range [34]. This group also hypothesized that a current, which is more sensitive to TTX than the normal rapid sodium current, might be present. Since the early 1980s, a growing number of biochemical and biophysical evidence suggest that in addition to $Na_V1.5$, neuronal and skeletal muscle sodium channel α-subunits are present in the heart.

In 1983, Renaud et al. [20] identified a large fraction of TTX-sensitive receptors in rat heart preparations. Although these results may reflect contamination by neuronal tissues