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Review

Genetic Na^+ channelopathies and sinus node dysfunction

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ABSTRACT

Voltage-gated Na^+ channels are transmembrane proteins that produce the fast inward Na^+ current responsible for the depolarization phase of the cardiac action potential. They play fundamental roles in the initiation, propagation, and maintenance of normal cardiac rhythm. Inherited mutations in *SCN5A*, the gene encoding the pore-forming α-subunit of the cardiac-type Na^+ channel, result in a spectrum of disease entities termed Na^+ channelopathies. These include multiple arrhythmic syndromes, such as the long QT syndrome type 3 (LQT3), Brugada syndrome (BrS), an inherited cardiac conduction defect (CCD), sudden infant death syndrome (SIDS) and sick sinus syndrome (SSS). To date, mutational analyses have revealed more than 200 distinct mutations in *SCN5A*, of which at least 20 mutations are associated with sinus node dysfunction including SSS. This review summarizes recent findings bearing upon: (i) the functional role of distinct voltage-gated Na^+ currents in sino-atrial node pacemaker function; (ii) genetic Na^+ channelopathy and its relationship to sinus node dysfunction.

Contents

1. Introduction

Conditions leading to sinus node dysfunction have considerable clinical importance. For example, sick sinus syndrome (SSS) manifesting as sinus bradycardia, sinus arrest and/or sino-atrial block is the most frequent worldwide clinical indication for pacemaker implantation (Mangrum and DiMarco, 2000). SSS may be associated with underlying cardiac disease but most commonly occurs in the elderly in the absence of apparent accompanying heart disease, although it can occur at any age (de Marneffe et al., 1993). Recent investigations have linked genetic ion channel defects with the familial sinus bradycardia syndromes (Benson et al., 2003; Groenewegen et al., 2003; Lei et al., 2007; Schulze-Bahr et al., 2003;

Abbreviations: AP, action potential; ATX-II, anemone toxin II (derived from *Anemonia sulcata*); AV, atrioventricular; BrS, Brugada syndrome; CCD, an inherited cardiac conduction defect; CT, crista terminalis; DAD, delayed afterdepolarization; EAD, early afterdepolarization; IVC, inferior vena cava; LQT3, long QT syndrome type 3; LQTS, long QT syndrome; PCCD, progressive cardiac conduction defect; RA, right atrial appendage; RT-PCR, real-time polymerase chain reaction; SA, sino-atrial; SEP, septum; SIDS, sudden infant death syndrome; SSS, sick sinus syndrome; SVC, superior vena cava; TTX, tetrodotoxin; WT, wild-type.

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Smits et al., 2005; Veldkamp et al., 2003). For example, inherited heterozygous mutations in *SCN5A* (Benson et al., 2003), the gene encoding the pore-forming α-subunit of the cardiac Na^+ channel, and *HCN4* (Milanesi et al., 2006; Schulze-Bahr et al., 2003), the gene encoding the hyperpolarization-activated cyclic nucleotide gated channel generating "funny" pacemaker current in cardiac pacemaker cells, have been linked to a rare, familial SSS. Functional characterization of these mutant channels associated with sinus node dysfunction has in turn provided a wealth of information emphasizing the sensitivity of cardiac rhythm to channel function and has provided new insights into the molecular mechanisms underlying sinus node dysfunction.

2. Voltage-gated Na^+ channels and sino-atrial node pacemaker function

Although voltage-dependent Na^+ channel currents have been recorded from sino-atrial (SA) node pacemaker cells (Cho et al., 2003; Honjo et al., 1996; Irisawa et al., 1993; Mangoni and Nargeot, 2001; Nathan, 1986), the possible contribution from Na^+ currents to SA node pacemaker function has long been remained uncertain until recently. Thus, Na^+ current does not occur in all pacemaker cells and in any case may inactivate at relatively positive potentials (Honjo et al., 1996; Irisawa et al., 1993; Nathan, 1986). In this section, we will highlight recent progress relevant to this issue.

2.1. Expression of voltage-gated Na^+ channels in the sino-atrial node

During the last decade, significant progress has been made in understanding the molecular structure of voltage-gated Na^+ channels (for reviews see Catterall, 2000; Catterall et al., 2003; Goldin, 2001; Goldin et al., 2000). It is now clear that these channels are composed of pore-forming α-subunits, with molecular weight of approximately 260 kDa, and associated auxiliary β-subunits of molecular weights around 36 kDa (Catterall, 2000; Goldin, 2001; Goldin et al., 2000). The expression of the pore-forming α-subunit alone is sufficient for functional Na^+ current expression, but the kinetics and voltage-dependence of channel gating are known to be modified by the presence or absence of β-subunits. The α-subunits are organized into four homologous domains (I–IV). Each contains six transmembrane α-helices (S1–S6) and an additional pore loop located between the S5 and S6 helices. Fig. 1 illustrates the predicted membrane structure topology of the α-subunit of the cardiac Na^+ channel, $Na_v1.5$. To date, ten α-subunits and four β-subunits have been identified (Goldin, 2001; Yu and Catterall, 2003). The various α-subunit isoforms are differentially expressed in different tissues and have distinct pharmacological properties (Goldin, 2001).

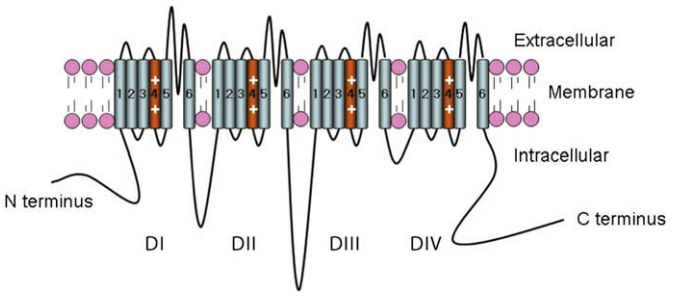

Fig. 1. The predicted membrane topology of the α-subunit of $Na_v1.5$. The four homologous domains (DI-DIV) of the α-subunit each contain 6 segments (marked 1–6) of which segments 5 and 6 are the pore-lining segments and the S4 helices serve as voltage sensors.

Recent investigations have also demonstrated that multiple α-subunits are co-expressed in cardiac tissues, in addition to the cardiac isoform $Na_v1.5$. These include several neuronal isoforms including $Na_v1.1$, $Na_v1.3$ and $Na_v1.6$ that are primarily expressed in the brain (Maier et al., 2003; Lei et al., 2004). In the SA node, there is a complex co-expression of multiple Na_v isoforms. Maier et al. (2003) showed that $Na_v1.5$ is absent from the central region of the SA node, whereas $Na_v1.1$ is expressed throughout the SA node and the surrounding atrial muscle in rat and mouse. It has been further confirmed that $Na_v1.1$ is present in the SA node. However, although $Na_v1.5$ is not expressed in central nodal cells, it is expressed in peripheral nodal cells (Lei et al., 2004) (Fig. 2). $Na_v1.3$ was also reported to be present in mouse SA node (Maier et al., 2003), but not in rabbit and rat SA node (Baruscotti et al., 1997; Maier et al., 2003). More recently, Haufe et al. (2005) demonstrated by using competitive RT-PCR and immunohistology that $Na_v1.1$, $Na_v1.2$ and $Na_v1.5$ are all expressed in canine SA node and atrioventricular (AV) node.

2.2. Physiological function of Na^+ channels in the sino-atrial node

Recent studies have further clarified the functional role of the distinct cardiac and neuronal type Na^+ channels in the SA node. Tetrodotoxin (TTX) at nanomolar concentrations that only inhibit TTX-sensitive neuronal Na^+ current slowed down the pacemaker rate of intact mouse hearts by ~65% (Maier et al., 2003), isolated SA nodes by 22 ± 8% (Lei et al., 2004) and isolated nodal cells by 15 ± 2% (Lei et al., 2004). Our study demonstrated that this TTX-sensitive neuronal Na^+ current was capable of activation within the normal voltages ranges shown by the pacemaker potential (Lei et al., 2004). As demonstrated in Fig. 3, action potentials were first recorded in current-clamp mode before switching to voltage-clamp. They were then used as the command waveforms *in the same cell* for current recording. After a steady pattern of current was obtained under control conditions, 50 nM TTX was applied. This concentration was sufficient to block TTX-sensitive neuronal Na^+ current, while exerting little effect on cardiac, TTX-resistant Na^+ current. This resulted in an increase in the net outward current due to block of the TTX-sensitive inward current during the action potential. The TTX-sensitive current during the action potential (AP) was then obtained by subtracting current in the presence of TTX from the control current that had been obtained in the absence of TTX. The TTX-sensitive Na^+ current started to activate at ~−50 mV, which is appropriate to the range of diastolic potentials. This is also consistent with the threshold of the TTX-sensitive Na^+ current measured with square voltage-clamp pulses (Lei et al., 2004). Together these findings were consistent with a role for TTX-sensitive Na^+ current carried by neuronal type Na^+ channels in the pacemaker function of the SA node (Lei et al., 2004).

Action potential propagation through the SA node, measured by the SA conduction time, would take place through the periphery of the SA node. The Na^+ current would also be expected to control such conduction as this would depend on both the upstroke velocity and amplitude of the AP, and both of these are dependent on Na^+ current. The SA node has been modelled using a concentric organization, containing small central and larger peripheral cells. In the latter cells, the density of TTX-resistant Na^+ current is greater than that of TTX-sensitive Na^+ current. Consequently in the periphery of the SA node, the dominant Na^+ current is likely to be TTX-resistant Na^+ current. This study next demonstrated that block of both TTX-sensitive and TTX-resistant Na^+ current by micromolar concentrations of TTX caused a slowing or even a block of SA node conduction from the leading pacemaker site in the centre of the SA node to the surrounding atrial muscle that takes place via the periphery of the SA node. These effects were not seen following