Cardiovascular Research 76 (2007) 381–389
Cardiovascular Research
www.elsevier.com/locate/cardiores

Roles and regulation of the cardiac sodium channel $Na_v1.5$: Recent insights from experimental studies

Hugues Abriel *

University of Lausanne, Department of Pharmacology and Toxicology and Service of Cardiology, Bugnon, 27, 1005 Lausanne, Switzerland

Received 31 May 2007; received in revised form 16 July 2007; accepted 29 July 2007
Available online 8 August 2007
Time for primary review 20 days

Abstract

During the past decade, $Na_v1.5$, the main voltage-gated Na^+ channel in the heart, has been shown to be involved in many cardiac diseases. Genetic variants in the gene *SCN5A*, encoding $Na_v1.5$, have been linked to various cardiac phenotypes, such as the congenital and acquired long QT syndromes, Brugada syndrome, conduction slowing, sick sinus syndrome, atrial fibrillation, and even cases of dilated cardiomyopathy. This unexpected phenotypic diversity may reflect that $Na_v1.5$ is not only restricted to the initiation of the action potential and rapid cardiac conduction, but may also be involved in other, not-yet elucidated, functions. Despite the fact that our understanding of the regulation of expression, localization, and function of $Na_v1.5$ is deepening, we are still far from a comprehensive view. Much of our current knowledge has been obtained by carrying out experiments using "cellular expression systems", e.g. host cells expressing exogenous $Na_v1.5$. Although very informative, these techniques are limited, in that $Na_v1.5$ is not expressed in the physiological cellular environment of a cardiac cell. Recently, however, there have been several studies published which used approaches closer to "normal" or pathological physiology.

In an attempt to summarize recently published data, this article will review the phenotypes of genetically-modified mouse strains where $Na_v1.5$ expression and activity are directly or indirectly modified, as well as the regulation of $Na_v1.5$ function using native cardiac myocytes. Despite obvious limitations, the reviewed studies provide an overview of the complex multi-factorial and multi-protein regulation of $Na_v1.5$.

Keywords: Sodium channel; Electrophysiology; Mouse models; Cardiomyocites; Congenital long QT syndrome; Brugada syndrome; Cardiac conduction

1. Introduction

The voltage-gated Na^+ channel $Na_v1.5$ initiates the cardiac action potential (AP) of the "working" myocardium, is essential for conduction of the electrical impulse, and is also known to control the AP duration [1]. More recently, its contribution to the sino-atrial node pacemaker function has also been demonstrated [2]. $Na_v1.5$ is the principal Na^+ channel isoform expressed in cardiomyocytes. Other isoforms of the Na_v family are also expressed in the heart, although their contribution to the cardiac physiology is still poorly understood [3]. In terms of its biophysical properties, $Na_v1.5$ can be found in three states: *closed* at resting membrane potential (about −85 mV), *open* upon depolarization, and in an *inactivated* non-conductive state. The transition between these states depends mainly on transmembrane voltage difference, time, and temperature. Recovery from the inactivated state occurs during repolarisation of the membrane during diastole. Fast depolarization of the myocyte (upstroke of the AP) and conduction both depend on the availability of $Na_v1.5$ (i.e. amount of channels in the closed state) [4]. Entry into the inactivated state is very fast (<1 ms) and for most channels, this inactivated state is very stable. It has been shown, however, that $Na_v1.5$ channels may re-open, thus generating a depolarizing inward current after the plateau phase of the AP [5]. This phenomenon may underlie the shortening of the AP duration caused by tetrodotoxin observed in Purkinje fibres and myocytes [6].

Since 1995, more than 170 naturally-occurring genetic variants in *SCN5A* (see www.fsm.it/cardmoc/), the gene coding for $Na_v1.5$, have been linked to cardiac disorders,

* Tel.: +41 21 6925364; fax: +41 21 6935355.
E-mail address: hugues.abriel@unil.ch.

0008-6363/$ - see front matter © 2007 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.cardiores.2007.07.019

such as congenital and drug-acquired long QT syndromes (LQTS), Brugada syndrome (BrS), conduction disorders, sudden infant death syndrome (SIDS), sinus dysfunction, atrial fibrillation [7,8], and dilated cardiomyopathy [9]. This long list of phenotypes may suggest that $Na_v1.5$ is not only restricted to the initiation and conduction of the AP, but may also be related to other more subtle functions.

$Na_v1.5$ is a glycosylated membrane protein with a molecular weight of ∼220 kDa and consists of 2015 or 2016 amino acids (depending on the splice variant) [10]. The protein is made up of four homologous domains (DI to DIV, Fig. 1), each with six transmembrane segments (S1 to S6). Three intracellular linker loops and both the N-and C-termini of the channel are cytoplasmic. The four S4 transmembrane segments are involved in activation gating of the channel (Fig. 1, in green), while a cluster of three hydrophobic amino acids in the III-IV linker, Ile-Phe-Met (IFM), are involved in fast inactivation gating (Fig. 1, red box). In cardiac cells, $Na_v1.5$ associates with partner proteins which may be anchoring/adaptor proteins, enzymes which interact with and modify the channel, and proteins modulating the biophysical properties of $Na_v1.5$ upon binding (reviewed in [11]). $Na_v1.5$ also interacts with β-subunits (∼30–35 kDa, β1 to β4-subunits, Fig. 1): one transmembrane-domain proteins involved in different aspects of $Na_v1.5$ function [12].

The precise localization of $Na_v1.5$ in cardiac cells is somewhat controversial. It is recognized that a pool of $Na_v1.5$ is located at the specialized cell-cell junctions known as the intercalated disks [13,14]. The localization of $Na_v1.5$ in lateral membranes and t-tubules, however, is still debated [14–17]. In dog myocytes, Na_v channels (most likely $Na_v1.5$) have also been observed in the endoplasmic reticulum [18].

During recent years, our understanding of the regulation of expression, localization, function and role of $Na_v1.5$ in diseases has grown rapidly. A large amount of this knowledge has been obtained by carrying out experiments using "cellular expression systems" (host cells) such as Xenopus oocytes and human embryonic kidney (HEK)-293 cells which "heterologously" express wild-type and mutant $Na_v1.5$ [19]. Although very informative, these techniques are limited by the fact that the sodium channel protein is not processed in its physiological cellular context. Studies using approaches closer to the "normal" or pathological physiology have recently been published. The scope of this review is restricted to the discussion of recent findings obtained by (1) investigating the phenotypes of genetically-modified mouse strains, where $Na_v1.5$ is directly or indirectly modified, and (2) studying the regulation of $Na_v1.5$ function using "homologous" expression of the channel in cardiac cells. For prior studies there are several excellent review articles [20–23].

2. Mouse models with altered function of $Na_v1.5$

Despite initial scepticism related to the fact that the cardiac electrophysiological characteristics of the mouse are strikingly different than those of humans [24], important and informative $Na_v1.5$-related studies using genetically-modified mouse models have recently been published.

2.1. $Na_v1.5$ knock-out mouse studies

Homozygous knock-out (KO) *Scn5a* mouse embryos die during mid-gestation, most likely due to the severe cardiac malformations identified [25]. This helps illustrate the essential role of $Na_v1.5$ in cardiac development. As one might expect, heterozygous KO mice (*Scn5a+/−*) mainly display slow atrial, atrio-ventricular (AV), and intra-ventricular

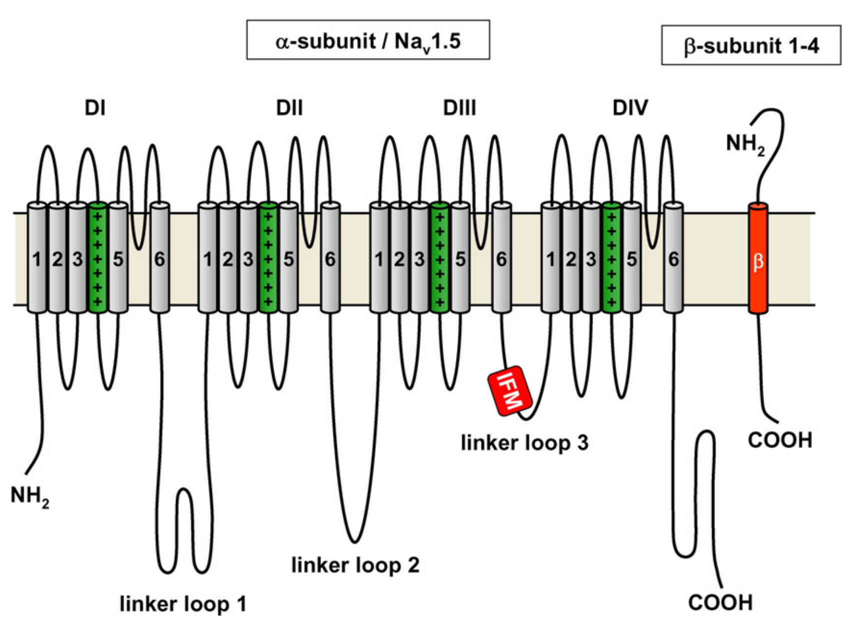

Fig. 1. Schematic membrane topology of $Na_v1.5$, the pore-forming subunit of the cardiac sodium channel and its associated β-subunits.

conduction, as well as increased inducibility of ventricular arrhythmias [25]. Following this initial report [25], several studies investigating the consequences of decreased $Na_v1.5$ expression were published. Royer and co-workers [26] reported that *Scn5a+/−* mice display an age-dependent deterioration of the global conduction properties associated with the manifestation of fibrosis in the ventricular myocardium. In certain aspects, this phenotype mimics Lenègre-Lev disease, a progressive cardiac conduction disorder [27]. These findings raised the question as to whether fibrosis might be the consequence of a loss of function of $Na_v1.5$, as recently suggested in humans in the context of BrS [28,29]. Fibrosis, as well as disruption of the cellular distribution of connexin-43, seems to underlie this age-dependent conduction slowing [30]. Recent evidence [31] shows that the slowed AV conduction in *Scn5a+/−* mice [26] depends on the expression of $Na_v1.5$ in AV node input and output regions. Finally, the role of $Na_v1.5$ in modulating sinus node automaticity has also been demonstrated in *Scn5a+/−* mice [32]. Altogether, these studies underline the importance of the Nav1.5-mediated inward current in cardiac automaticity and conduction.

2.2. $Na_v1.5$ knock-in or transgenic mouse models mimicking human diseases

The generation of knock-in (KI) or transgenic mice harbouring mutant *SCN5A* alleles is a powerful method for examining the consequences of a human *SCN5A* mutation in a physiological context. Three such mouse lines that have been recently produced are discussed below.

2.2.1. SCN5A mutation Δ1505-1507KPQ

Most of the mutations of $Na_v1.5$ found in congenital LQTS patients (defining the LQTS type 3) alter the fast inactivation process of the channel [33], thereby inducing a persistent inward depolarizing current during the AP plateau phase. Consequently, the repolarisation of the AP is delayed and leads to congenital LQTS. The deletion of three amino acids (Δ1505-1507KPQ) of $Na_v1.5$ was the first *SCN5A* mutation which lead to a Nav1.5 persistent current [34]. In 2001, the first KI ΔKPQ mouse model was generated [35]. This study confirmed that in myocytes, LQT-3 mutant $Na_v1.5$ channels generate a persistent current and prolong the AP; while in *vivo* the expression of mutant channels, increase the QT interval duration of the ECG. Increased arrhythmogenicity, illustrated by spontaneous polymorphic ventricular tachycardia (VT), was also reported [35]. More recently, a similar ΔKPQ mouse line was created [36] and the results obtained were consistent with the previous study [35]. These two mouse lines allowed the investigation of anti-arrhythmic procedures and drugs. Results showed that, consistent with clinical data, β-blockers failed [36]; whereas mexiletine (Na_v blocker) and rapid pacing could suppress VT [37]. It is mainly thought that the LQT-3 arrhythmogenic phenotype depends on early after-depolarisations (EAD) caused by the prolonged AP [38], however, in a recent study [39] the occurrence of so-called delayed after-depolarisations (i.e. after full repolarisation of the AP) was clearly demonstrated in myocytes of the ΔKPQ mouse. This finding suggests that this additional mechanism may contribute to the severity of arrhythmias seen in LQT-3. The LQT-3 genotype, although less frequent, is often more lethal [40]. Finally, a puzzling finding of these two first studies [35,36] is that the I_{Na} recorded from individual KI myocytes was about 2-fold larger that wild-type controls. This was not the case, however, in another recent study [39]. The reason for this discrepancy remains to be clarified.

2.2.2. SCN5A mutation 1795insD

SCN5A mutations lead not only to many different pathologic phenotypes [9], but also to combinations of these phenotypes, known as "overlap syndromes" [41–43]. The reasons for these overlapping phenotypes are not completely understood. It is thought, however, that at a slow heart rate the late-current dependent AP prolongation is responsible for LQTS, whereas at a high heart rate conduction slowing (because of reduced availability of Nav1.5) underlies the BrS phenotype. Remme and co-workers [44] recently generated a KI mouse line expressing the 1795insD *SCN5A* mutation (insertion of an aspartic acid in locus 1795, 1798 in mouse *Scn5a*), which has been shown to cause both LQTS and BrS in one large Dutch family [43]. The detailed phenotyping of this mouse line showed that expression of the 1795insD channel recapitulates many of the pathological features seen in patients, such as: bradycardia, conduction slowing because of decreased I_{Na}, and delayed repolarisation caused by the mutation-induced persistent I_{Na}. This study clearly illustrates the benefits of mouse models for the study of specific human arrhythmias resulting from $Na_v1.5$ dysfunction.

2.2.3. SCN5A mutation N1325S

The *SCN5A* mutation N1325S causes LQT-3 syndrome [45], and like many similar mutations, leads to an increased persistent current [46]. The generation of a transgenic mouse line enabling demonstration of the phenotypes of LQTS, VT, and sudden death [46], permitted researchers to investigate alternative arrhythmogenic mechanisms [45]. Experiments using isolated myocytes and performing AP recordings showed that, at heart rates with cycle length ≤ 500 ms, AP alternans and instability (i.e. large variability in AP duration) were clearly observed [45]. Interestingly, the Ca^{2+}channel blocker verapamil reduced this AP instability, suggesting an involvement of intracellular Ca^{2+} dysregulation in this phenomenon. Altogether, these studies illustrate that the mechanisms underlying arrhythmogenicity in LQT-3 may be multifold and mutation dependent.

2.3. Dystrophin-deficient mice

Similar to other ion channels, $Na_v1.5$ has been reported to be part of the dystrophin multi-protein complex [47]. Recently, using a "pull-down" approach, our group showed that $Na_v1.5$ is interacting via adaptor proteins, called syntrophins, with dystrophin [48]. This interaction depends on the PDZ domain-binding motif on the C-terminus of $Na_v1.5$ [11]. In dystrophin-deficient mice (mdx5cv), an animal model of Duchenne muscular dystrophy, $Na_v1.5$ protein level was reduced in ventricular lysates, leading to reduced cellular I_{Na} and conduction defects that were documented via ECGs. The detailed mechanisms by which a lack of dystrophin reduces the expression of $Na_v1.5$ protein without altering the mRNA level [48], remain to be explored. Whether the decreased expression of $Na_v1.5$ plays a direct role in, or is the consequence of, the degenerative cardiomyopathy seen in Duchenne patients is still unanswered. Another intriguing question raised by these findings is related to the fact that dystrophin has been shown to be absent from the intercalated disks of human [49] and rat [50] cardiomyocytes, where a fraction of $Na_v1.5$ is clearly present [14]. These observations suggest that at least two pools of $Na_v1.5$ channels co-exist at the plasma membrane of cardiac cells. One pool, localized in lateral membranes, may belong to the dystrophin complex; whereas another pool resides at the intercalated disks. In the latter pool, the PDZ domain-binding motif of $Na_v1.5$ may be associated with other proteins, either via syntrophin (e.g. utrophin) or other PDZ-domain proteins. Baba and co-workers [16] recently showed that dog cardiomyocytes isolated from infarcted zones displayed a reduced I_{Na} density, associated with a marked loss of the $Na_v1.5$ staining in the lateral membranes only. In contrast, the $Na_v1.5$ staining remained unchanged in the intercalated disks. This leads one to believe that this lateral dystrophin-dependent pool of $Na_v1.5$ may be more sensitive to specific pathological insults (in this case ischemia) than the intercalated-disk pool.

2.4. *Ca^{2+}/calmodulin-dependent protein kinase II*

Phosphorylation of $Na_v1.5$ by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) has recently been reported [51]. CaMKII is a widely expressed serine/threonine kinase which transduces intracellular Ca^{2+}increase into phosphorylation of multiple proteins, including ion channels [52]. Importantly, CaMKIIδc has been shown to be up-regulated in human and animal heart failure models (reviewed in [53]). Wagner and co-workers [51] showed that CaMKIIδc is co-localized and can be co-immunoprecipited with $Na_v1.5$ in cardiac tissues, although the mode of interaction has not yet been investigated. Over-expression of CaMKIIδc in rabbit myocytes and transgenic mice altered several biophysical properties of $Na_v1.5$. In summary, CaMKII-dependent phosphorylation of $Na_v1.5$ shifted the steady-state inactivation curve towards negative voltages in a Ca^{2+}-dependent manner, slowed the recovery from inactivation, and markedly increased the persistent current (as seen with LQT-3 mutant $Na_v1.5$ channels). Overall, at rapid heart rate, these alterations decrease the availability of I_{Na}; while at slower heart rate, the persistent current-dependent prolongation of repolarisation predominates. Interestingly, this biophysical phenotype is similar to the one seen in patients and mice carrying the 1795insD mutation (see 2.2.2). These results are supported by the observation that VT could be generated in mice over-expressing CaMKII while showing signs of heart failure [51]. Overall, it is likely that CaMKII plays a prominent role in heart failure-dependent arrhythmias involving $Na_v1.5$. However, more direct evidence is needed in order to confirm this hypothesis.

2.5. *Transgenic over-expression of $Na_v1.5$*

What are the consequences of over-expressing $Na_v1.5$? Despite the fact that the cardiac $Na_v1.5$ transcript and protein levels were increased by about 10-fold in a *SCN5A* transgenic mouse line [54], no increase of I_{Na} and AP duration of atrial and ventricular cells was observed. These surprising findings suggest that there may be intrinsic mechanisms avoiding "overloading" of the cardiac cell membrane with $Na_v1.5$. Does it mean that cardiac cells are able to "sense" the number of $Na_v1.5$ at the cell membrane? Or, is the cell membrane under normal conditions "saturated" with $Na_v1.5$? These are open questions that merit further study. Finally, these $Na_v1.5$ over-expressing mice displayed a very mild shortening of the P-wave and PQ-interval duration [54]; a finding that is not easily explained due to the lack of effects at the cellular level.

2.6. *Transgenic mice over-expressing the protein phosphatase calcineurin*

Protein phosphatase calcineurin plays a central role in cardiac hypertrophy [55]. Interestingly, progressive conduction defects leading to complete cardiac conduction block, associated with episodes of VT, were observed in transgenic mice over-expressing a constitutive active form of calcineurin [56]. This phenotype was later shown to be due to a profound reduction of I_{Na} [57]. This I_{Na} decrease was age-dependent in that at 50 days of age, the recorded current was virtually abolished. Guo and co-workers [57] addressed the issue of how mice can survive with such a small I_{Na} in their discussion. This strong I_{Na} down-regulation can also be obtained by infecting neonatal myocytes with adenovirus encoding a constitutive active form of calcineurin [57]. Interestingly, there was clear evidence that intracellular Ca^{2+} homeostasis was involved in this process since thapsigargin, ryanodine and the Ca^{2+} chelating agent AM-BAPTA were all successful in counteracting the effects of calcineurin over-expression. Involvement of PKC in this process was also suggested because bisindolylmaleimide I antagonized the effects of calcineurin, a finding that is consistent with previous observations showing PKC-dependent down-regulation of I_{Na} [58]. The biochemical expression of $Na_v1.5$ was not altered in calcineurin-mice; whereas non-stationary noise analysis (a biophysical approach to evaluate the number of channels active at the cell surface) clearly showed a reduced density of Na^+channels [57]. These *in vivo* results indicate that intracellular Ca^{2+} and PKC are involved in regulation of $Na_v1.5$ trafficking, but the detailed molecular mechanisms are not yet understood.

2.7. Transgenic mice over-expressing Snail, a transcription factor

The Snail genes are transcription factors involved in the regulation of expression of many genes; in particular, many of the proteins of the cell-cell junctions are repressed by Snail [59]. In a mouse model of cardiac-specific over-expression of Snail, the phenotype of severe dilated cardiomyopathy and significant conduction defects was observed [60]. The I_{Na} recorded in the cardiomyocytes of these transgenic hearts was only about 10% of the wild-type current. The authors also showed that Snail protein is capable of interacting with the promoter region of *SCN5A* resulting in repression of expression in a heterologous expression system. Although suggested to be the case in humans [61], it remains to be determined whether the decreased expression of $Na_v1.5$ is the cause of the dilated cardiomyopathy seen in this mouse model.

3. Molecular regulation of $Na_v1.5$ in cardiomyocytes

In the following sections, recent results regarding molecular aspects of $Na_v1.5$ regulation in native cardiomyocytes are discussed.

3.1. Ankyrin proteins bind to and regulate $Na_v1.5$

Ankyrin proteins, encoded by three distinct genes *ANK1-3*, anchor membrane proteins to the actin and spectrin cytoskeleton [62]. In the heart, both ankyrin-B (encoded by *ANK2*) and ankyrin-G (encoded by *ANK3*) are expressed [62], and both are reported to be involved in different types of cardiac arrhythmias. In humans, many genetic variants of *ANK2* are linked to diverse pathological phenotypes such as LQTS type 4 [63], drug-induced LQTS, and sudden cardiac death, giving rise to the “ankyrin-B cardiac syndrome” [64]. However, there is no direct evidence that $Na_v1.5$ is regulated by ankyrin-B, even though it was reported that in neonatal mouse cardiomyocytes KO for ankyrin-B, cardiac Na^+channels display late openings similar to the ones seen in $Na_v1.5$ LQT-3 mutant channels [65]. In contrast, ankyrin-G directly interacts with a specific ankyrin-binding motif of the linker loop between domain II and III [66]. Mohler and co-workers described a BrS patient with a *SCN5A* mutation (E1053 K) in this motif which disrupted the interaction between $Na_v1.5$ and ankyrin-B [17]. Using an elegant technique involving lentiviral vectors, the authors [17] were able to express tagged $Na_v1.5$ channels in adult rat myocytes. Whereas wild-type channels trafficked normally to the intercalated disks and lateral membranes, E1053 K channels remained in the cytoplasm of infected myocytes [17]. These results suggest that ankyrin-G may not only act as an anchoring protein for $Na_v1.5$, but that it may also participate in its correct trafficking and sorting. These interesting finding are not yet fully understood and demand further study.

3.2. Role of caveolin-3 in regulating $Na_v1.5$

Caveolin-3 is an important component of small invaginations of the plasma membrane called caveolae, in which a variety of signalling molecules and ion channels are enriched [67]. *CAV3*, the gene encoding caveolin-3, is known to be mutated in neuromuscular diseases such as limb-girdle muscular dystrophy and rippling-muscle disease [68], and more recently in patients with congenital LQTS (LQT-9) [69] and SIDS [70]. $Na_v1.5$ can be co-immunoprecipitated with caveolin-3 from native tissue [71], and also when co-expressed in HEK293 cells [69]. Furthermore, both proteins are co-localized [69,71,72]. Interestingly, dystrophin is also a component of caveolae [73]. This raises the possibility that the interaction with $Na_v1.5$ may be indirect via proteins of the dystrophin multi-protein complex, which are mainly expressed in the lateral membranes. The role of the $Na_v1.5$/caveolin-3 interaction is somewhat puzzling. Co-expression of $Na_v1.5$ with the mutants of caveolin-3 found in LQTS and SIDS patients significantly increased the persistent late current in HEK293 cells, a molecular phenotype consistent with the clinical features [69,70]. In rat cardiac myocytes, however, a robust rapid increase of I_{Na} in response to β-adrenergic stimulation by isoproterenol, (PKA-independent due to the presence of a PKA inhibitor) was completely abolished by anti-caveolin 3 antibodies dialysed into the myocytes [71]. Shibata and co-workers [72] proposed that a pool of $Na_v1.5$ channels are located in caveolar compartments that are not in contact with the extracellular side of the myocytes. β-adrenergic stimulation, in a PKA-independent but Gαs-dependent manner, opens the caveolae and thus increases the number of $Na_v1.5$ channels at the cell surface. This attractive model demands further study at the molecular level, since the role of caveolin-3 and its interaction with $Na_v1.5$ remains unclear.

Finally, in transgenic mice with a Duchenne muscle dystrophy phenotype where caveolin-3 is over-expressed, a decrease in dystrophin and its associated proteins are observed not only in muscle but also in the heart [74]. The cardiac phenotype of these mice is characterized by a fibrotic cardiomyopathy with prolongation of the QRS interval similar to the heterozygous *SCN5A*-KO mice. Altogether, these results illustrate the important, but not yet completely understood, role of caveolar $Na_v1.5$.

3.3. Na_v β-subunits regulating $Na_v1.5$

Na_v channels have been shown to be associated with regulatory β-subunits [12], one-segment transmembrane proteins (Fig. 1). Four genes encoding voltage-gated sodium channel β-subunits (β1–β4) are found in the human genome. The roles of these β-subunits are multiple and often, controversial (as is the case for Na_v1.5 — reviewed in [12]). This problem may be due to the fact that groups have been testing the β-subunits in different types of cellular expression systems. Among the different functions of β-subunits, Isom's group showed that when using mouse total cardiac or cardiomyocyte lysates [75] β1 and β2 subunits associate with ankyrin-G and ankyrin-B. It was previously shown that the β1/ankyrin interactions are regulated by the phosphorylation state of a tyrosine residue located in the intracellular part of the protein [76]. Using a phosphospecific antibody, it was shown that tyrosine-phosphorylated β1 are located at the intercalated disks, and that non-phosphorylated proteins are in the lateral membranes [75]. In addition, Na_v1.5 channels of the intercalated disk-pool were shown to not only colocalize with phosphotyrosin-β1, but also with connexin-43 (a well-known intercalated disk protein) and N-cadherin [75]. A more detailed discussion of this potential multiprotein complex can be found in [12].

Thus far, *in vivo* evidence for a Na_v β-subunit-dependent regulation of Na_v1.5 is scarce, but the findings reported in two recent studies suggest it plays an important role. In a large family with congenital LQTS, a mutation in the gene coding for β4 Na_v subunit was found to co-segregate with the long QT phenotype [77]. In HEK293 cells, co-expression of mutant β4 significantly increased the Nav1.5-dependent persistent current, consistent with the LQTS phenotype [77]. In another study investigating the phenotype of β1 null mice, it was reported that they exhibit a significantly longer QT interval compared to wild-type mice [78]. Further investigation of this interesting phenotype is pending.

3.4. Protein kinase A (PKA)-dependent regulation of Na_v1.5

In cardiac cells, PKA is mainly activated upon β-adrenergic receptor stimulation, leading to an increase in intracellular cyclic AMP [79]. The role of this pathway in regulating Na_v1.5, respectively I_{Na}, has been studied for many years (reviewed in [80]), resulting in many published discordant results. In more recent studies [81–84], it has been consistently reported that upon PKA activation an acute time-dependent increase of I_{Na} was observed, with slight or no alterations in its biophysical characteristics. Boyden's group [81] published the only recent study using cardoiomyocytes to investigate this phenomenon. By incubating dog cardiomyocytes with a PKA-activating cocktail (membrane-permeable cAMP, IBMX and forskolin), the authors observed a 30% increase in I_{Na}; whereas cells close to the infarcted zone showed a reduced increase. Chloroquine pre-treatment blunted this PKA-dependent increase, leading the authors to conclude that part of these effects depend on "vesicular trafficking" [81]. PKA-dependent enhancement of trafficking of Na_v1.5 can also be monitored in HEK293 cells expressing GFP-tagged channels [82]. A detailed analysis using these cells suggested the presence of a sub-membrane population of Na_v1.5 redistributing into the plasma membrane upon PKA activation. The authors proposed that the location of these channels beneath the membrane and their PKA-dependent translocation may be consistent with the opening of "silent" caveolae hypothesis [72] (see 3.2). Although very appealing, the molecular aspects of the PKA-dependent trafficking model as well as the effects of adrenergic stimulation in regulating I_{Na} are still largely unknown.

3.5. Tyrosine phosphorylation of Na_v1.5

Functional regulation of ion channels via tyrosine phosphorylation has been shown to be very important [85]. In two recent studies [86,87], tyrosine phosphorylation of native cardiac Na_v1.5 was demonstrated using anti-phosphotyrosine antibodies probing immunoprecipitated Na_v1.5. Moreover, it was found that isolated rat cardiomyocytes showed increased I_{Na} upon stimulation by epidermal growth factor receptor, a receptor tyrosine kinase. This response was potentiated by orthovanadate, a tyrosine phosphatase inhibitor [87]. Interestingly Ahern and co-workers [86] reported that in HEK293 cells the tyrosine kinase Fyn modulated several biophysical properties of Na_v1.5. In addition, our group recently reported [88] that protein tyrosine phosphatase PTPH1 interacts with the same PDZ-domain binding motif of Na_v1.5 (as described for syntrophin proteins-see above). It is possible that the proper function of Na_v1.5 is dependent on the balance between protein tyrosine kinase and phosphatase activities in cardiac cells. However, the physiological relevance of these observations remains to be fully determined.

3.6. Regulation of Na_v1.5 by the adenosine monophosphate-activated protein kinase (AMPK)

AMPK is a serine/threonine protein kinase involved in sensing the metabolic status of the cell [89]. Several recent studies (reviewed in [90]) demonstrated that mutations in the γ2 regulatory subunit of AMPK lead to a complex cardiac phenotype displaying, alone or in combination, ventricular pre-excitation (Wolff–Parkinson–White syndrome), conduction defect, and cardiac hypertrophy. Light and co-workers over-expressed a constitutive active form of AMPK in rat ventricular myocytes [91] and observed, among other alterations, a significant increase of the persistent I_{Na} with a prolongation of the AP leading to EADs. Whether AMPK-dependent regulation of Na_v1.5 can be seen *in vivo* has yet to be studied.

4. Conclusions and perspectives

Since the beginning of cellular electrophysiology studies, the cardiac I_{Na} has been the focus of many scientists and laboratories [92]. During the past decade, this field has received a strong impetus due to the description of many naturally-occurring mutations in the Na_v1.5 gene which lead to severe cardiac disease. Initially, most of these studies were performed using "expression systems", and in many cases the mutation-induced alterations of $Na_v1.5$ were easily elucidated and extrapolated to their clinical phenotypes. This approach, however, is not without limitations. For instance, although the BrS E1053K mutant channels displayed no trafficking defect in HEK293 cells, they were not routed to the cell membrane in cardiomyocytes [17]. Another illustrative example is the case of the BrS mutation T1620M; depending on the expression system used (oocytes vs. HEK293 cells), the molecular phenotypes were found to be contradictory to one another [93]. We are now in a new era where there is an important effort undertaken to develop experimental models that more closely mimic human physiological condition. Two main approaches have been used, the results of which have been reviewed in this article. These studies have been investigating genetically-modified mouse models and used sophisticated cell biology techniques applicable to isolated cardiomyocytes. Both techniques remain very labour intensive, time consuming, and are mastered by only a few laboratories. It is without doubt, however, that many of the questions remaining about the role and regulation of $Na_v1.5$ will only be adequately addressed by using such modern genetic, molecular, and cell biology techniques. A few of the unsolved issues are for example: the physiological relevance of the proteins shown to associate and regulate $Na_v1.5$ in mammalian cell lines, i.e. fibroblast growth factor homologous factor 1B [94], 14-3-3 protein [95], calmodulin [96,97], and Nedd4 ubiquitin ligases [98]; and also the possibility that $Na_v1.5$ is part of different multi-protein complexes located at the intercalated disks or the lateral membranes. It can be forseen that these future studies will help elucidate the multiple and complex roles of $Na_v1.5$ in cardiac physiology and disease.

Acknowledgments

Supported in part by the Swiss National Science Foundation (PP00-110638/1 SNF-professorship). We are grateful Dr. A. Felley for her many suggestions on this manuscript, to N. Skarda for her editorial help, as well as to the members of the laboratory of H. Abriel for their essential contributions to the projects described in this article. We would also like to apologise to the many investigators whose studies were noted cited because of space limitation.

References

[1] Nerbonne JM, Kass RS. Molecular Physiology of Cardiac Repolarization. Physiol Rev 2005;85:1205–53.
[2] Lei M, Zhang H, Grace AA, Huang CL. SCN5A and sinoatrial node pacemaker function. Cardiovasc Res Jun 1 2007;74(3):356–65.
[3] Haufe V, Chamberland C, Dumaine R. The promiscuous nature of the cardiac sodium current. J Mol Cell Cardiol Mar 2004;42(3):469–77.
[4] Kleber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. Physiol Rev 2004;84:431–88.
[5] Tateyama M, Liu H, Yang AS, Cormier JW, Kass RS. Structural effects of an LQT-3 mutation on heart Na+ channel gating. Biophys J 2004;86:1843–51.
[6] Coraboeuf E, Deroubaix E, Coulombe A. Effect of tetrodotoxin on action potentials of the conducting system in the dog heart. Am J Physiol Heart Circ Physiol 1979;236:H561–7.
[7] Laitinen-Forsblom PJ, Makynen P, Makynen H, Yli-Mayry S, Virtanen V, Kontula K, et al. SCN5A mutation associated with cardiac conduction defect and atrial arrhythmias. J Cardiovasc Electrophysiol 2006;17:480–5.
[8] Chen LY, Ballew JD, Herron KJ, Rodeheffer RJ, Olson TM. A common polymorphism in SCN5A is associated with Lone Atrial Fibrillation. Clin Pharmacol Ther 2007;81:35–41.
[9] Wilde AAM, Bezzina CR. Genetics of cardiac arrhythmias. Heart 2005;91:1352–8.
[10] Makielski JC, Ye B, Valdivia CR, Pagel MD, Pu J, Tester DJ, et al. A ubiquitous splice variant and a common polymorphism affect heterologous expression of recombinant human SCN5A heart sodium channels. Circ Res 2003;93:821–8.
[11] Abriel H, Kass RS. Regulation of the voltage-gated cardiac sodium channel Nav1.5 by interacting proteins. Trends Cardiovasc Med 2005;15:35–40.
[12] Meadows LS, Isom LL. Sodium channels as macromolecular complexes: implications for inherited arrhythmia syndromes. Cardiovasc Res 2005;67:448–58.
[13] Cohen SA. Immunocytochemical localization of rH1 sodium channel in adult rat heart atria and ventricle: presence in terminal intercalated disks. Circulation 1996;94:3083–6.
[14] Maier SKG, Westenbroek RE, McCormick KA, Curtis R, Scheuer T, Catterall WA. Distinct subcellular localization of different sodium channel {alpha} and {beta} subunits in single ventricular myocytes from mouse heart. Circulation 2004;109:1421–7.
[15] Brette F, Orchard CH. Density and sub-cellular distribution of cardiac and neuronal sodium channel isoforms in rat ventricular myocytes. Biochem Biophys Res Commun 2006;348:1163–6.
[16] Baba S, Dun W, Cabo C, Boyden PA. Remodeling in cells from different regions of the reentrant circuit during ventricular tachycardia. Circulation 2005;112:2386–96.
[17] Mohler PJ, Rivolta I, Napolitano C, Lemaillet G, Lambert S, Priori SG, et al. Nav1.5 E1053K mutation causing Brugada syndrome blocks binding to ankyrin-G and expression of Nav1.5 on the surface of cardiomyocytes. Proc Natl Acad Sci U S A 2004;101:17533–8.
[18] Zimmer T, Biskup C, Dugarmaa S, Vogel F, Steinbis M, Bohle T, et al. Functional expression of GFP-linked human heart sodium channel (hH1) and subcellular localization of the a subunit in HEK293 cells and dog cardiac myocytes. J Membr Biol 2002;186:1–12.
[19] Dice MS, Kearl T, Ruben PC. Methods for studying voltage-gated sodium channels in heterologous expression systems. Methods Mol Med 2006;129:163–85.
[20] Marban E, Yamagishi T, Tomaselli GF. Structure and function of voltage-gated sodium channels. J Physiol (Lond) 1998;508(Pt 3):647–57.
[21] Balser JR. Structure and function of the cardiac sodium channels. Cardiovasc Res 1999;42:327–38.
[22] Grant AO. Molecular biology of sodium channels and their role in cardiac arrhythmias. Am J Med 2001;110:296–305.
[23] Herfst LJ, Rook MB, Jongsma HJ. Trafficking and functional expression of cardiac Na+ channels. J Mol Cell Cardiol 2004;36: 185–93.
[24] Nerbonne JM, Nichols CG, Schwarz TL, Escande D. Genetic manipulation of cardiac K(+) channel function in mice: what have we learned, and where do we go from here? Circ Res 2001;89:944–56.
[25] Papadatos GA, Wallerstein PM, Head CE, Ratcliff R, Brady PA, Benndorf K, et al. Slowed conduction and ventricular tachycardia after targeted disruption of the cardiac sodium channel gene Scn5a. Proc Natl Acad Sci U S A 2002;99:6210–5.
[26] Royer A, van Veen TA, Le Bouter S, Marionneau C, Griol-Charhbili V, Leoni AL, et al. Mouse model of SCN5A-linked hereditary Lenegre's disease: age-related conduction slowing and myocardial fibrosis. Circulation 2005;111:1738–46.
[27] Schott JJ, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M, et al. Cardiac conduction defects associate with mutations in SCN5A. Nat Genet 1999;23:20–1.

[28] Frustaci A, Priori SG, Pieroni M, Chimenti C, Napolitano C, Rivolta I, et al. Cardiac histological substrate in patients with clinical phenotype of brugada syndrome. Circulation 2005;112:3680–7.
[29] Coronel R, Casini S, Koopmann TT, Wilms-Schopman FJG, Verkerk AO, de Groot JR, et al. Right ventricular fibrosis and conduction delay in a patient with clinical signs of brugada syndrome: a combined electrophysiological, genetic, histopathologic, and computational study. Circulation 2005;112:2769–77.
[30] van Veen TAB, Stein M, Royer A, Le Quang K, Charpentier F, Colledge WH, et al. Impaired impulse propagation in Scn5a-knockout mice. Combined contribution of excitability, connexin expression, and tissue architecture in relation to aging. Circulation 2005;112:1927–35.
[31] Yoo S, Dobrzynski H, Fedorov VV, Xu SZ, Yamanushi TT, Jones SA, et al. Localization of Na+ channel isoforms at the atrioventricular junction and atrioventricular node in the rat. Circulation 2006;114: 1360–71.
[32] Lei M, Goddard C, Liu J, Leoni AL, Royer A, Fung SSM, et al. Sinus node dysfunction following targeted disruption of the murine cardiac sodium channel gene Scn5a. J Physiol (Lond) 2005;567:387–400.
[33] Kass RS, Moss AJ. Long QT syndrome: novel insights into the mechanisms of cardiac arrhythmias. J Clin Invest 2003;112:810–5.
[34] Bennett PB, Yazawa K, Makita N, George Jr AL. Molecular mechanism for an inherited cardiac arrhythmia. Nature 1995;376:683–5.
[35] Nuyens D, Stengl M, Dugarmaa S, Rossenbacker T, Compernolle V, Rudy Y, et al. Abrupt rate accelerations or premature beats cause life-threatening arrhythmias in mice with long-QT3 syndrome. Nat Med 2001;7:1021–7.
[36] Head CE, Balasubramaniam R, Thomas G, Goddard CA, Lei M, Colledge WH, et al. Paced electrogram fractionation analysis of arrhythmogenic tendency in DeltaKPQ Scn5a mice. J Cardiovasc Electrophysiol 2005;16:1329–40.
[37] Fabritz L, Kirchhof P, Franz MR, Nuyens D, Rossenbacker T, Ottenhof A, et al. Effect of pacing and mexiletine on dispersion of repolarisation and arrhythmias in DeltaKPQ SCN5A (long QT3) mice. Cardiovasc Res 2003;57:1085–93.
[38] Clancy CE, Rudy Y. Linking a genetic defect to its cellular phenotype in a cardiac arrhythmia. Nature 1999;400:566–9.
[39] Fredj S, Lindegger N, Sampson KJ, Carmeliet P, Kass RS. Altered Na+ channels promote pause-induced spontaneous diastolic activity in long QT syndrome type 3 myocytes. Circ Res Nov 24 2006;99(11):1225–32.
[40] Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866–74.
[41] Grant AO, Carboni MP, Neplioueva V, Starmer CF, Memmi M, Napolitano C, et al. Long QT syndrome, Brugada syndrome, and conduction system disease are linked to a single sodium channel mutation. J Clin Invest 2002;110:1201–9.
[42] Kyndt F, Probst V, Potet F, Demolombe S, Chevallier JC, Baro I, et al. Novel SCN5A mutation leading either to isolated cardiac conduction defect or Brugada syndrome in a large French family. Circulation 2001;104:3081–6.
[43] Bezzina C, Veldkamp MW, van Den Berg MP, Postma AV, Rook MB, Viersma JW, et al. A single Na(+) channel mutation causing both long-QT and brugada syndromes. Circ Res 1999;85:1206–13.
[44] Remme CA, Verkerk AO, Nuyens D, van Ginneken ACG, van Brunschot S, Belterman CNW, et al. Overlap syndrome of cardiac sodium channel disease in mice carrying the equivalent mutation of human SCN5A-1795insD. Circulation 2006;114:2584–94.
[45] Yong SL, Ni Y, Zhang T, Tester DJ, Ackerman MJ, Wang QK. Characterization of the cardiac sodium channel SCN5A mutation, N1325S, in single murine ventricular myocytes. Biochem Biophys Res Commun 2006;352:378–83.
[46] Tian XL, Yong SL, Wan X, Wu L, Chung MK, Tchou PJ, et al. Mechanisms by which SCN5A mutation N1325S causes cardiac arrhythmias and sudden death in vivo. Cardiovasc Res 2004;61: 256–67.
[47] Gee SH, Madhavan R, Levinson SR, Caldwell JH, Sealock R, Froehner SC. Interaction of muscle and brain sodium channels with multiple members of the syntrophin family of dystrophin-associated proteins. J Neurosci 1998;18:128–37.
[48] Gavillet B, Rougier JS, Domenighetti AA, Behar R, Boixel C, Ruchat P, et al. Cardiac sodium channel Nav1.5 is regulated by a multiprotein complex composed of syntrophins and dystrophin. Circ Res 2006;18: 407–14.
[49] Kaprielian RR, Stevenson S, Rothery SM, Cullen MJ, Severs NJ. Distinct patterns of dystrophin organization in myocyte sarcolemma and transverse tubules of normal and diseased human myocardium. Circulation 2000;101:2586–94.
[50] Stevenson SA, Cullen MJ, Rothery S, Coppen SR, Severs NJ. High-resolution en-face visualization of the cardiomyocyte plasma membrane reveals distinctive distributions of spectrin and dystrophin. Eur J Cell Biol 2005;84:961–71.
[51] Wagner S, Dybkova N, Rasenack EC, Jacobshagen C, Fabritz L, Kirchhof P, et al. Ca/calmodulin-dependent protein kinase II regulates cardiac Na channels. J Clin Invest Dec 2006;116(12):3127–38.
[52] Soderling TR, Chang B, Brickey D. Cellular signaling through multifunctional Ca2+/Calmodulin-dependent protein kinase II. J Biol Chem 2001;276:3719–22.
[53] Maier LS, Bers DM. Calcium, calmodulin, and calcium-calmodulin kinase II: heartbeat to heartbeat and beyond. J Mol Cell Cardiol 2002;34:919–39.
[54] Zhang T, Yong SL, Tian XL, Wang QK. Cardiac-specific over-expression of SCN5A gene leads to shorter P wave duration and PR interval in transgenic mice. Biochem Biophys Res Commun 2007;355: 444–50.
[55] Molkentin JD. Calcineurin-NFAT signaling regulates the cardiac hypertrophic response in coordination with the MAPKs. Cardiovasc Res 2004;63:467–75.
[56] Dong D, Duan Y, Guo J, Roach DE, Swirp SL, Wang L, et al. Overexpression of calcineurin in mouse causes sudden cardiac death associated with decreased density of K+channels. Cardiovasc Res 2003;57:320–32.
[57] Guo J, Zhan S, Somers J, Westenbroek RE, Catterall WA, Roach DE, et al. Decrease in density of INa is in the common final pathway to heart block in murine hearts overexpressing calcineurin. Am J Physiol Heart Circ Physiol 2006;291:H2669–79.
[58] Murray KT, Hu NN, Daw JR, Shin HG, Watson MT, Mashburn AB, et al. Functional effects of protein kinase C activation on the human cardiac Na+ channel. Circ Res 1997;80:370–6.
[59] Barrallo-Gimeno A, Nieto MA. The Snail genes as inducers of cell movement and survival: implications in development and cancer. Development 2005;132:3151–61.
[60] Hesse M. Dilated Cardiomyopathy is Associated with Reduced Expression of the Cardiac Sodium Channel Scn5a. Cardiovasc Res Aug 1 2007;75(3):498–509.
[61] Olson TM, Michels VV, Ballew JD, Reyna SP, Karst ML, Herron KJ, et al. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. JAMA J Am Med Assoc 2005;293:447–54.
[62] Cunha SR, Mohler PJ. Cardiac ankyrins: essential components for development and maintenance of excitable membrane domains in heart. Cardiovasc Res 2006;71:22–9.
[63] Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Guatimosim S, DuBell WH, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. Nature 2003;421:634–9.
[64] Mohler PJ, Le Scouarnec S, Denjoy I, Lowe JS, Guicheney P, Caron L, et al. Defining the cellular phenotype of "Ankyrin-B Syndrome" variants. Human ANK2 variants associated with clinical phenotypes display a spectrum of activities in cardiomyocytes. Circulation 2007;115:432–41.
[65] Chauhan VS, Tuvia S, Buhusi M, Bennett V, Grant AO. Abnormal cardiac Na(+) channel properties and QT heart rate adaptation in neonatal ankyrin(B) knockout mice. Circ Res 2000;86:441–7.
[66] Lemaillet G, Walker B, Lambert S. Identification of a conserved ankyrin-binding motif in the family of sodium channel alpha subunits. J Biol Chem 2003;278:27333–9.

[67] Maguy A, Hebert TE, Nattel S. Involvement of lipid rafts and caveolae in cardiac ion channel function. Cardiovasc Res 2006;69:798–807.
[68] Williams TM, Lisanti MP. The Caveolin genes: from cell biology to medicine. Ann Med 2004;36:584–95.
[69] Vatta M, Ackerman MJ, Ye B, Makielski JC, Ughanze EE, Taylor EW, et al. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. Circulation 2006;114:2104–12.
[70] Cronk LB, Ye B, Kaku T, Tester DJ, Vatta M, Makielski JC, et al. Novel mechanism for sudden infant death syndrome: persistent late sodium current secondary to mutations in caveolin-3. Heart Rhythm 2007;4:161–6.
[71] Yarbrough TL, Lu T, Lee HC, Shibata EF. Localization of cardiac sodium channels in caveolin-rich membrane domains: regulation of sodium current amplitude. Circ Res 2002;90:443–9.
[72] Shibata EF, Brown TL, Washburn ZW, Bai J, Revak TJ, Butters CA. Autonomic regulation of voltage-gated cardiac ion channels. J Cardiovasc Electrophysiol 2006;17(Suppl 1):S34–42.
[73] Doyle DD, Goings G, Upshaw-Earley J, Ambler SK, Mondul A, Palfrey HC, et al. Dystrophin associates with caveolae of rat cardiac myocytes: relationship to dystroglycan. Circ Res 2000;87:480–8.
[74] Aravamudan B, Volonte D, Ramani R, Gursoy E, Lisanti MP, London B, et al. Transgenic overexpression of caveolin-3 in the heart induces a cardiomyopathic phenotype. Hum Mol Genet 2003;12:2777–88.
[75] Malhotra JD, Thyagarajan V, Chen C, Isom LL. Tyrosine-phosphorylated- and nonphosphorylated-sodium channel beta 1 subunits are differentially localized in cardiac myocytes. J Biol Chem 2004;279:40748–54.
[76] Malhotra JD, Koopmann MC, Kazen-Gillespie KA, Fettman N, Hortsch M, Isom LL. Structural requirements for interaction of sodium channel beta 1 subunits with ankyrin. J Biol Chem 2002;277:26681–8.
[77] Medeiros-Domingo A, Kaku T, Tester DJ, Iturralde-Torres P, Itty A, Ye B, et al. SCN4B-encoded sodium channel β4 subunit in congenital long-QT syndrome. Circulation 2007;116:134–42.
[78] Meadows LS, Chen C, Speelman AI, Malhotra JD, Isom LL. Characterization of cardiac sodium channel function in b1 subunit null mice. Society for Neuroscience; 2004. 262.9, Abstract.
[79] Bers DM. Cardiac excitation-contraction coupling. Nature 2002;415: 198–205.
[80] Schreibmayer W. Isoform diversity and modulation of sodium channels by protein kinases. Cell Physiol Biochem 1999;9:187–200.
[81] Baba S, Dun W, Boyden PA. Can PKA activators rescue Na+ channel function in epicardial border zone cells that survive in the infarcted canine heart? Cardiovasc Res 2004;64:260–7.
[82] Hallaq H, Yang Z, Viswanathan PC, Fukuda K, Shen W, Wang DW, et al. Quantitation of protein kinase A-mediated trafficking of cardiac sodium channels in living cells. Cardiovasc Res Nov 1 2006;72(2):250–61.
[83] Nuss HB, Marban E, Balke CW, Goldman L, Aggarwal R, Shorofsky SR, et al. Whether “Slip-Mode Conductance” occurs. Science 2000;284.
[84] Zhou J, Yi J, Hu N, George Jr AL, Murray KT. Activation of protein kinase A modulates trafficking of the human cardiac sodium channel in Xenopus oocytes. Circ Res 2000;87:33–8.
[85] Davis MJ, Wu X, Nurkiewicz TR, Kawasaki J, Gui P, Hill MA, et al. Regulation of ion channels by protein tyrosine phosphorylation. Am J Physiol Heart Circ Physiol 2001;281:H1835–62.
[86] Ahern CA, Zhang JF, Wookalis MJ, Horn R. Modulation of the cardiac sodium channel NaV1.5 by Fyn**,** a Src family tyrosine kinase. Circ Res 2005;01.
[87] Liu H, Sun HY, Lau CP, Li GR. Regulation of voltage-gated cardiac sodium current by epidermal growth factor receptor kinase in guinea pig ventricular myocytes. J Mol Cell Cardiol 2007;42:760–8.
[88] Jespersen T, Gavillet B, van Bemmelen MX, Cordonier S, Thomas MA, Staub O, et al. Cardiac sodium channel Nav1.5 interacts with and is regulated by the protein tyrosine phosphatase PTPH1. Biochem Biophys Res Commun 2006;348:1456–63.
[89] Arad M, Seidman CE, Seidman JG. AMP-activated protein kinase in the heart: role during health and disease. Circ Res 2007;100:474–88.
[90] Gollob MH. Glycogen storage disease as a unifying mechanism of disease in the PRKAG2 cardiac syndrome. Biochem Soc Trans 2003;31:228–31.
[91] Light PE, Wallace CH, Dyck JR. Constitutively active adenosine monophosphate-activated protein kinase regulates voltage-gated sodium channels in ventricular myocytes. Circulation 2003;107:1962–5.
[92] Fozzard HA. Cardiac sodium and calcium channels: a history of excitatory currents. Cardiovasc Res 2002;55:1–8.
[93] Baroudi G, Carbonneau E, Pouliot V, Chahine M. SCN5A mutation (T1620M) causing brugada syndrome exhibits different phenotypes when expressed in xenopus oocytes and mammalian cells. FEBS Lett 2000;467:12–6.
[94] Liu CJ, Dib-Hajj SD, Renganathan M, Cummins TR, Waxman SG. Modulation of the cardiac sodium channel Nav1.5 by fibroblast growth factor homologous factor 1B. J Biol Chem 2003;278:1029–36.
[95] Allouis M, Le Bouffant F, Wilders R, Peroz D, Schott JJ, Noireaud J, et al. 14-3-3 is a regulator of the cardiac voltage-gated sodium channel Nav1.5. Circ Res 2006;01.
[96] Tan HL, Kupershmidt S, Zhang R, Stepanovic S, Roden DM, Wilde AA, et al. A calcium sensor in the sodium channel modulates cardiac excitability. Nature 2002;415:442–7.
[97] Kim J, Ghosh S, Liu H, Tateyama M, Kass RS, Pitt GS. Calmodulin mediates Ca2+ sensitivity of sodium channels. J Biol Chem 2004;279: 45004–12.
[98] van Bemmelen MX, Rougier JS, Gavillet B, Apotheloz F, Daidie D, Tateyama M, et al. Cardiac voltage-gated sodium channel Nav1.5 is regulated by Nedd4-2 mediated ubiquitination. Circ Res 2004;95: 284–91.