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An Emerging Antiarrhythmic Target: Late Sodium Current

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Abstract: The cardiac late sodium current ($I_{Na,L}$) has been in the focus of research in the recent decade. The first reports on the sustained component of voltage activated sodium current date back to the seventies, but early studies interpreted this tiny current as a product of a few channels that fail to inactivate, having neither physiologic nor pathologic implications. Recently, the cardiac $I_{Na,L}$ has emerged as a potentially major arrhythmogenic mechanism in various heart diseases, attracting the attention of clinicians and researchers. Research activity on $I_{Na,L}$ has exponentially increased since Ranolazine, an FDA-approved antianginal drug was shown to successfully suppress cardiac arrhythmias by inhibiting $I_{Na,L}$. This review aims to summarize and discuss a series of papers focusing on the cardiac late sodium current and its regulation under physiological and pathological conditions. We will discuss critical evidences implicating $I_{Na,L}$ as a potential target for treating myocardial dysfunction and cardiac arrhythmias.

Keywords: Late sodium current, cardiac sodium channel, arrhythmias.

1. INTRODUCTION

Cardiac arrhythmias are one of the primary causes of death and a major public health problem. However, anti-arrhythmic drug therapies using ion channel blockers led to conflicting results. Many seemingly promising drugs turned out to be proarrhythmic. Clinical experiences by many physicians sum up to two important observations: (1) Ion channels blockers are risky, and some exacerbate arrhythmias. (2) Relatively successful drugs, such as beta blockers and amiodarone, modulate not only ion channels but also Ca^{2+} homeostasis. Implantable cardioverters and catheter ablation opened a new dimension in the reduction of arrhythmia related mortality. However, these techniques, being introduced during the last decade, are not widely applicable in several cases of life threatening arrhythmias. Therefore, pharmacological therapy remains the most frequently applied medical intervention in controlling arrhythmias and heart failure.

The late sodium current, initially seen as a tiny sustained tail of sodium current, was out of the focus of research for a long time, but immediately gained increasing interest since it was linked to cardiac diseases. Upregulation of the plateau sodium current has been implicated in multiple inherited or acquired arrhythmia syndromes or structural heart diseases. At the same time, inhibition of the currents was demonstrated to prevent or reduce arrhythmic activity in multiple pathologic models. Exponential growth in the number of research papers and comprehensive reviews [1-6] published in the last few years indicates the great expectation on $I_{Na,L}$ as a new, potential therapeutic target. At the present, the greatest limiting factor for the progress of this field is the lack of specific $I_{Na,L}$ inhibitors. Development of highly specific $I_{Na,L}$ blockers will facilitate research and provide archetype for a new class of antiarrhythmic drugs.

2. BRIEF HISTORICAL REMARKS ON CARDIAC LATE SODIUM CURRENT

Dubois and Bergman reported their observations on a persistent, tetrodotoxin (TTX) sensitive current present in frog Ranvier node in 1975. The current was interpreted as a fraction of voltage activated sodium current that failed to inactivate [7], which put forththe concept of $I_{Na,L}$. In 1979, Coraboeuf *et al*. observed that low concentration of TTX shortened canine Purkinje AP without reducing the amplitude of '*the normal rapid sodium current*' [8]. The authors suggested two critical features for $I_{Na,L}$ in their publication: a) there is a sodium current flowing during entire plateau of cardiac AP b) involvement of non-cardiac voltage dependent sodium channels. In accordance with these results *Attwell et al.* reported the presence of a TTX sensitive non inactivating sodium current at negative membrane potentials in sheep Purkinje fibers [9]. They suggested that the 'window current' mechanism is involved in generatingthe sustained sodium current and predicted that this current might exert large effect on action potential (AP) duration. In 1989, Kiyosue and Makita conducted a systematic study on the sodium current in guinea pig ventricular myocytes [10]. They identified three different types of sodium channel activities, two of them present longer than 100 ms following depolarization, thus casted as 'late' activity. They characterized a '*late scattered mode*' and a '*burst mode*' to be responsible for $I_{Na,L}$ (discussed below), and showed that the *'normal'* (transient) channel activation is followed by late activity in less than 4% of patches. They confirmed the observation by *Coraboeuf et al*.on the AP shortening effect of TTX, and suggested that $I_{Na,L}$ contributes to regulation of the AP duration. The central question in these early studies was whether or not this relatively small Na^+ current can play a significant role in shaping the AP duration. In the following years $I_{Na,L}$ was found upregulated by hypoxia, free radicals or ischemic metabolites [11-13]. The finding that elevated $I_{Na,L}$ was associated with heart diseases and linked to increased propensity of arrhythmias markedly boosted research activities in this field[14-17]. Recent experimental data obtained by ^{self}AP-clamp [18] indicate that earlier data obtained using squre pulse voltage-clamp technique might have underestimated the magnitude of $I_{Na,L}$ [19, 20]. Furthermore, recent publication by Horvath *et al*. [18] show that the magnitude of $I_{Na,L}$ is comparable with that of major potassium currents, making it a cardinal player in shaping the AP morphology.

3. THE IDENTITY OF LATE NA^+ CURRENT: ONE CURRENT WITH MULTIPLE MECHANISMS?

Mammalian cells express several isoforms of voltage-dependent sodium channels distinguishable by their kinetics, unit conductance

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and drug sensitivity. The dominant isoform in cardiac tissues is the $Na_v1.5$ (also called *h1* or *skm II*) encoded by the gene *SCN5A*, which is relatively insensitive to tetrodotoxin, saxitoxin and μ-conotoxin [21, 22]. The pore forming, large α subunit is associated with four auxiliary ß$_1$through ß$_4$ subunits which are known to modify the kinetics and voltage dependence of the channel. ß$_1$ but not ß$_2$ subunit was shown to slow down the inactivation of cardiac sodium current, thus to facilitate $I_{Na,L}$ [23]. In contrast to this, ß$_3$ subunit was found to accelerate the inactivation, reducing $I_{Na,L}$ [24]. At resting membrane potential, the channel is in non-conductive state, but sufficient depolarization ($V_{1/2}$: -40/-50 mV) activates the channel to conductive state [25-27].

3.1. Different Single Channel Activity Patterns May Contribute to $I_{Na,L}$

Upon changes of membrane potential sodium channels undergo a sequence of conformational changes. Following significant depolarization the majority of closed channels open in less than two milliseconds and then inactivate within next 2 ms [28, 29]. Transition from inactivated state to closed state is promoted by repolarization. If membrane remains depolarized the first opening can be followed by reopening. Maltsev & Undrovinas studied single sodium channels and observed and modelled three distinct types of activity present in human ventricular myocytes [30]. In *Transient Mode* (TM) the first opening is followed by 5-10 rapid reopening resulted from flip-flops between open and inactive state of the channel (Fig. **1**). This repetitive activity is terminated within less than 40 ms when channel absorbed in a second inactive state, resulting in rapid decline seen in the ensemble current ($I_{Na,L}$). The current magnitude drops below 10% of the peak within 3 ms. The *Transient Mode* contributes to ~90% of the peak sodium current , but 20 ms later it inactivates and contribute to less than 1% of the total Na^+ current. This gating mode alone adequately explains the $I_{Na,T}$ (0-5 ms) of the peak sodium current but cannot explain the sustained $I_{Na,L}$ seen during the AP plateau. The second gating mode that contributes to the early phase or *Burst Mode* (BM) is characterized by sustained openings with brief closing periods (Fig. **1**). Increased transition rate from inactivated to open state and reduced probability toward the second inactivated state causes long lasting (100-300 ms) single channel activity before terminated by the absorbing state. These non-inactivating bursts had been known to exist in both skeletal and cardiac muscle and were referred to as slow, non-inactivating, or "cloudburst" currents [31-33]. Facilitation of *Burst Mode* were reported from cardiac muscles after chemical intervention and termed 'failure of inactivation' [34]. Channels display *Burst Mode* at very low probability generating only a tiny current. Hence, its contribution is negligible to $I_{Na,L}$ during the first 2-5 ms following the upstroke. However, as the *Transient Mode* component of I_{Na} decays following the peak, the relative contribution of *Burst Mode* to total current can grow as high as 50%. *Burst Mode* current then declines and 200-300 ms later it is replaced by the third gating mode referred as *Late Scattered Mode* (LSM). *Late Scattered Mode* can be derived from *Transient Mode* by reducing transition rates from inactive to open and second inactive (absorbing) state. It is characterized by sparse reopening for an extended period being as long as 500-1000 ms (Fig. **1**).

The involvement of the three different gating modes in I_{Na} changes dynamically during AP. Based on their contribution to sodium current it is possible to separate three phases or time period. The early phase of AP (0-5 ms) is dominated exclusively by *Transient Mode*; BM and LSM are negligible. This is followed by an intermediate phase of AP (5-20 or 5-40 ms) where all three gating modes are present with steeply reducing weight of TM. The late phase of I_{Na} (referred as $I_{Na,L}$) starts 20-40 ms after the AP upstroke and maintained by *Burst Mode* and *Late Scattered Mode*, and then *Late Scattered Mode* becomes the only gating mode shaping the late sodium current. Shifts in the relative magnitudes of the different gating modes caused by channel mutations or pathologic conditions have been implicated in cardiac electric disorders [23, 35-43]. Targeted pharmacological modulation of different gating modes is proposed to exert cardioprotective and antiarrhythmic effects [44-46].

3.2. The Window Current

The "window" region is the voltage range where the steady state activation and inactivation curves of sodium channels overlap. In the window current voltage range, channels can recover from inactivation and reopen. This flip-flop between active and inactive states can provide a steady-state current if membrane potential is held within this sensitive voltage range. When the identity of $I_{Na,L}$ is discussed in literature, the flip-flopping of the Na channel in the

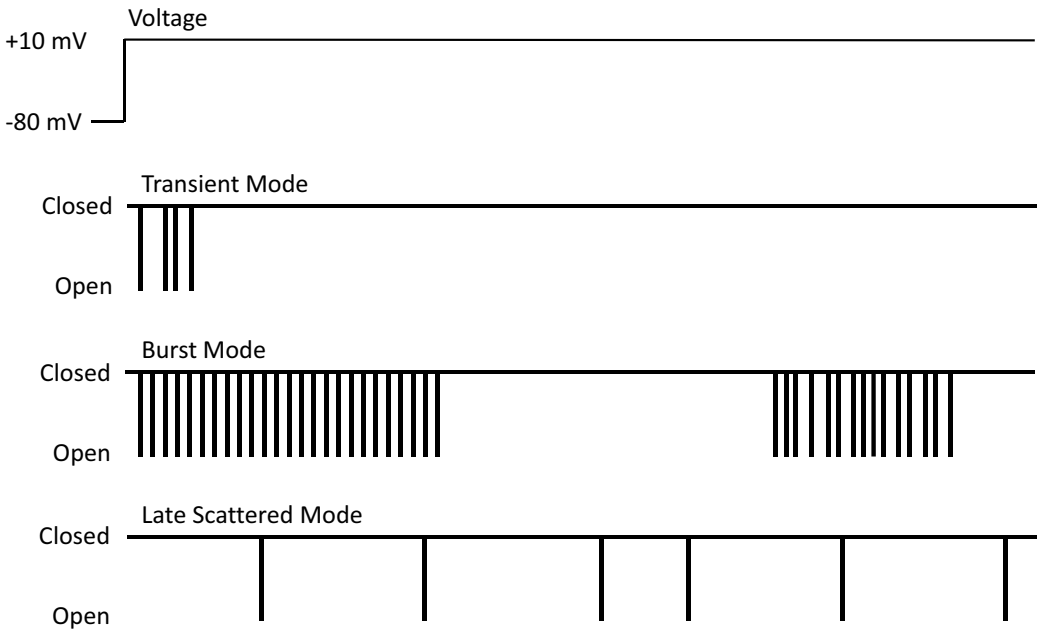

Fig. (1). Schematic illustration for different channel activity patterns contributing to late sodium current.

window region is usually the first mechanism used to explain the origin of sustained plateau sodium current [1-4]. The window mechanism seems like a plausible resolution to seemingly incompatible rapid inactivation of the sodium channels seen in voltage clamp experiments under rectangular command steps and the remarkably persistent sodium current during a several hundred milliseconds long AP plateau. However, while no experimental observation is known to question the existence of window mechanism, its contribution to $I_{Na,L}$ might be limited because of the voltage range where plateau is found. The center of the window region occurs around -60 mV, far below the plateau voltage (about 0 mV) in the ventricular myocytes of most species [2, 47]. In addition, the window current is very small under normal conditions (the maximum is less than 5% of I/I_{max} [25, 47-49]. Therefore, the window current is unlikely to be a major contributor to the late Na^+ current. Furthermore, experimental observations by *Beyder et al.* indicate that shear stress can shift the window current significantly to more negative voltage range [50]. Since our present knowledge on the position and with of window is based on electrophysiologic data obtained in unloaded cardiomyocytes, we can assume that the contribution of window to $I_{Na,L}$ is even less than predicted by current models. Nevertheless, it is possible that mutations or pathologic regulation of the channel might shift the activation or inactivation curve and alter the magnitude and voltage range of the window current [14].

3.3. Non-Equilibrium Gating

Different gating modes and the concept of window current can describe the behavior of sodium current elicited with square pulse voltage clamp. However, the sodium channels in functioning cardiac cells are exposed to dynamically changing voltage. Experimental data show that $I_{Na,L}$ is greatly facilitated when evoked with repolarizing voltage ramp or AP shape command [18-20]. *Clancy et al.* proposed a new mechanism named 'non-equilibrium gating' that can explain these observations [19]. According to this concept, recovery from inactivation is modulated by dynamically changing (non-equilibrium) voltage. The probability for reopening is increased during hyperpolarizing ramps resulting in facilitation of the activation transition. The novelty in this hypothesis is that the transition rate from a given state is modulated by the voltage trajectory the channel experienced beforehand. Hence, kinetic parameters of the channel are influenced by its short-time history. *Magyar et al.* provided strong experimental evidence to support the non-equilibrium gating hypothesis. They demonstrated that the open probability of the sodium channel is higher during voltage ramp than that observed with constant (rectangular or square pulse) voltage command, and the sodium current duration depends on the duration of ramp [20]. Furthermore, indirect evidence supporting this hypothesis were provided by *Horvath et al.* when they showed that the magnitude of $I_{Na,L}$ is comparable to those of major potassium currents, and the $I_{Na,L}$ current profile is determined by the voltage profile of AP in ventricular myocytes [18]. These observations led them to the conclusion that non-equilibrium gating is the chief factor determining the profile of TTX sensitive current during AP [18]. Non-equilibrium gating theory does not preclude the involvement of other gating modes in $I_{Na,L}$. All the mechanisms discussed in this session might coexist and contribute to shaping the profile of sodium current during AP. Since different gating modes are assumed to have different drug sensitivities or affinities [44, 51, 52] understanding the mechanism behind $I_{Na,L}$ can help to develop new antiarrhythmic strategies.

3.4. Non-cardiac sodium channels in the heart

Association of ECG abnormalities to epilepsy [53, 54] and myotonic disorders [55, 56] raised the possibility that the same sodium channels responsible for hereditary diseases of nervous system or skeletal muscles might also cause repolarization abnormalities in the heart. Later, several 'non cardiac' isoforms were found in cardiac tissue by functional tests based on voltage dependency and drug sensitivity in different species [38, 57-59]. Using RT-PCR or immunocytochemistry the expression of $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, $Na_v1.4$ and $Na_v1.6$ were detected in the hearts of multiple species [59-64]. According to the report of *Westenbroek et al.*, non-cardiac isoforms represent a substantial fraction (23%) of the total number of sodium channels in mouse heart [61]. Moreover, the distributions of different isoforms show characteristic patterns. While the cardiac isoform $Na_v1.5$ is localized preferentially to the sarcolemma including intercalated disks, it is absent from T-tubules; $Na_v1.1$ and $Na_v1.3$ (non-cardiac) isoforms are found to be localized to the T-tubules and absent from the cell surface. Brette *et al.* showed that the density of the cardiac sodium channel isoform (in channels/μm^2) is 13 and 10 at the cell surface and at the t-tubules, respectively. In contrast, the cell surface and t-tubule densities for neuronal sodium currents are 0.3 and 2.5 [65]. $Na_v1.4$ and $Na_v1.6$ showed low level surface staining. These data indicate that cardiac and non-cardiac isoforms of sodium channels may have different roles in the electrical excitation of cardiac cells. While the cardiac isoform is likely responsible for the cell-to-cell propagation of electric signal, the primary role of non-cardiac isoforms may be to couple the electric signal to calcium dynamics [60, 61]. How, such functional distinction was questioned by earlier work of Malhotra *et al.* who observed colocalization of $Na_v1.1$ and $Na_v1.5$ isoforms in rat myocardium [66].

The presence of non-cardiac isoforms in cardiac muscle naturally raises the question: what is the contribution of these non-cardiac sodium channels to total sodium current, especially to $I_{Na,L}$? To address this question, Biet *et al.* presented data suggesting that the contribution of non-cardiac sodium channels to the peak I_{Na} is between 5-10%, but 44% of $I_{Na,L}$ is generated by non-cardiac isoforms [57]. This observation has been confirmed by Yang *et al.* reporting that $Na_v1.8$ provide the 38% of $I_{Na,L}$ [58]. Considering the different kinetics, voltage and drug sensitivity of cardiac and non-cardiac voltage regulated sodium channels, as well as the distinct localization of different isoforms within the cardiac cell, these observations open a new direction in the exploration of physiological and pathological roles of $I_{Na,L}$. Research for isoform specific sodium channel inhibitors might provide a new strategy in antiarrhythmic therapy.

4. THE PHYSIOLOGY OF LATE SODIUM CURRENT

Several key ion currents delicately shape the plateau of cardiac action potential. To understand the interplay of currents and voltage during the plateau phase it is important to note that (1) the currents flowing in this phase are small relative to those that govern the upstroke and terminal repolarization, (2) the algebraic sum of the currents is small. The latter accounts for repolarization rate being close to zero during phase two [67]. Because the impedance of the cell membrane is high during the AP plateau phase and the magnitudes of the currents are inherently small, even subtle changes in any current can have a large impact on AP morphology. Additionally, the plateau currents I_{Kr} and I_{Ks} are sensitive to changes in membrane potential near the plateau voltage. This synergistic interplay between currents and voltage during the AP plateau phase have significant impact on the time course of terminal repolarization, and thus the AP duration [68].

4.1. Contribution of Late Sodium Current to Cardiac Electric Activity

Most of our current knowledge on the electrophysiology of $I_{Na,L}$ originates from the experiments employing rectangular pulse voltage clamp and the computer simulations based on those data. These results predicted a tiny flat current during the entire length of AP. Because of its small magnitude, the contribution of $I_{Na,L}$ to shaping AP under physiologic conditions was a subject of debate. Nevertheless two lines of new experimental evidence indicate that the late sodium current significantly affect the AP morphology. First, TTX

shortened the AP [8, 10]; and second, facilitation of $I_{Na,L}$ lengthened the AP [18, 69]. Furthermore, an increasing number of observations indicate that the magnitude of $I_{Na,L}$ was markedly underestimated in earlier reports. When using a ramp or AP shaped voltage clamp command, there is a substantial increase in the $I_{Na,L}$ current magnitude [19, 20]. Recent publication employing ^{self}AP-clamp technique indicates that the magnitude of the current during plateau is comparable to those of delayed rectifier potassium currents [18].

When cardiac sodium current is measured by rectangular command, the late component is not clearly distinguishable from $I_{Na,T}$, and it is often fitted by multiexponential function to separate the late component as a smooth continuation of the decaying early phase. When $I_{Na,L}$ is recorded under AP command, two major type of profiles are observed. In the first case the current magnitude decays monotonically; this profile was observed in dog and predicted by some of the models [70-72]. In the second type, the decay of $I_{Na,T}$ is followed by a slow current accumulation during the plateau, then it reaches a peak before the terminal repolarization of AP and declines rapidly toward zero when membrane potential returns to the resting level. This saddle-like profile was reported from human [73], canine [74], and guinea pig heart [18, 75]. These differences might arise from variances of AP shape in different species, but the impact of methodological differences cannot be excluded.

I_{Na} is a key player in propagation of cardiac electric activation in the myocardium [64, 76] and in less extent to pacemaker activity especially in young age [77]. Due to its contribution to AP duration, $I_{Na,L}$ has strong influence in determining QT interval of the ECG. Increased $I_{Na,L}$ is associated with lengthened QT interval (Long QT syndrome) and increased risk for arrhythmias [48, 78-83]. In accordance, inhibiting $I_{Na,L}$ was shown to shorten QT interval [84, 85]. Mutations causing facilitation of late sodium current are also associated with increased QT dispersion [53, 84]. How increased $I_{Na,L}$ leads to increased QT dispersion is not completely understood, but transmural heterogeneity of sodium channels is probably also involved [74, 86]. QT dispersion is determined routinely in clinical cardiology and regarded as one of the most valuable predictor for arrhythmias [87, 88]. Thus, increased repolarization inhomogeneity due to pathologic $I_{Na,L}$ might provide the substrate for arrhythmias caused by sodium channel mutations. Other forms of electric disturbances are also linked to pathologic sodium channel function such as Brugada syndrome [15, 89-94], slow impulse propagation [25, 95, 96], familiar atrial fibrillation [97, 98] and sick sinus syndrome [99, 100]. Cases, where sodium channel mutations were associated with cardiomyopathy were reported often with electric disturbances [101-103]. The link between altered channel function and structural diseases has not been established. However, these cases indicate that altered ionic balance may lead to structural heart diseases via modulation of genetic regulation.

4.2. Transmural Heterogeneity of $I_{Na,L}$

It is well known that transmural differences in ionic currents densities and AP shape are present in the ventricles [104-107]. Differences in sodium current magnitude between epicardial and endocardial cells were observed in canine and murine heart [74, 86, 108]. In addition, $I_{Na,L}$ was found larger in M cells than in the epicardial or endocardial region of canine ventricular wall contributing to the transmural differences in AP parameters. M cells are also known to display steeper rate dependence of AP than either epicardial or endocardial cells [109-111]. These data indicate a significant contribution of $I_{Na,L}$ to rate adaptation of AP length. This hypothesis is supported by earlier observations of Nuyens *et al*. who reported that increased $I_{Na,L}$ results in increased lengthening of AP duration at low pacing rate [112]. The issue was addressed by Guo *et al*. in a systematic study where they demonstrated that the AP lengthening induced by low pacing rate was increased when $I_{Na,L}$ was facilitated with Anemonia toxin (ATX-II) [113]. By contrast, inhibition of $I_{Na,L}$ with TTX reduced the AP duration sensitivity to pacing rate. Based on these data they concluded that $I_{Na,L}$ plays a key role in rate adaptation of AP duration; this conclusion has been confirmed by others [114, 115]. The involvement of late sodium current in rate adaptation can explain why $I_{Na,L}$ facilitation caused by mutant sodium channel increases the risk for arrhythmias following frequency changes [112].

The connection between $I_{Na,L}$ and arrhythmias is further supported by Lowe *et al*. [79] who found that $I_{Na,L}$ magnitude is higher in female mice compared to males and concluded that this difference contributes to higher arrhythmia susceptibility of females. The increased susceptibility of females to arrhythmias may be further compounded by reduced repolarization reserve and larger intramyocardial inhomogeneity of calcium and potassium currents in females [116-123].

4.3. $I_{Na,L}$ and Calcium Homeostasis of Cardiac Cells

Sodium channels contribute to total Na^+ entry into cardiac cells in significant extent [124, 125]. In spite of the seemingly small magnitude of $I_{Na,L}$, there is a consensus that when facilitated, the contribution of the sustained component to total Na^+ entry is comparable to that of the $I_{Na,T}$ [3, 6]. It is well documented that $I_{Na,L}$ facilitation results in increase of cytosolic sodium concentration, and it's specific inhibition can prevent sodium accumulation in cardiac myocytes [126-128]. Beyong its impact on the sodium homeostasis of cardiac cells, $I_{Na,L}$ is also implicated in modulation of the calcium homeostasis. Increased cytosolic Na^+ level leads to elevated cytosolic calcium concentration which is known to cause positive inotropic response [126, 129]. Calcium homeostasis in linked to $I_{Na,L}$ through multiple mechanisms.

4.3.1. $I_{Na,L}$ facilitates Ca^{2+} Influx via L-type Calcium Channels

As an inward current $I_{Na,L}$ lengthens AP and elevates the plateau voltage. The longer and higher depolarization increases the amount of Ca^{2+} entering to the cytoplasm through the L-type calcium channel. The profile of L-type calcium current (LTCC) during AP was a subject of debate for long time. Model simulations based on experimental data from traditional rectangular pulse voltage clamp experiments predicted divergent dynamics during AP. Some of the models predicted that LTCC is present only under early plateau then it declines [130, 131]. According to these models, AP lengthening should not alter Ca^{2+} entry in significant extent. Later, using action potential clamp technique it was well documented that L-type calcium current is present during the entire AP plateau phase and declines with the terminal repolarization in all mammalian models studied [107, 132-135]. Therefore, lengthening the AP should significantly increase the amount of Ca^{2+} entry via L-type calcium channels. What prevents the inactivation of L-type calcium current during plateau is not completely understood, but reopening of inactivated channels has been demonstrated during long depolarization [135, 136]. Another possible mechanism for sustained calcium current could be the window current. The crossing point for activation and inactivation curves is between -20 to 0 mV allowing a subpopulation of L-type calcium channels to flip-flop between open and inactive state [73, 137, 138]. Another mechanism that could maintain calcium current during plateau is the non-equilibrium gating mechanism discussed earlier with relation to sustained sodium current [2, 19, 20]. However, this possibility has not been tested experimentally. In summary, when $I_{Na,L}$ prolongs AP, Ca^{2+} influx is facilitated.

4.3.2. Slip Mode Conductance: Reexamining an Old Paradigm

The Lederer group published an interesting paper in the Science in 1998 where they raised the possibility of Ca^{2+} entry through TTX sensitive sodium channels [139]. They claimed that the selectivity of sodium channel can substantially reduce following PKA activation enabling Ca^{2+} to permeate as readily as Na^+. The idea was not completely new, Ca^{2+} permeation through sodium channels in the absence of Na^+ was reported previously [140]. However, subse-

quent works produced contradictory observations and suggested that TTX sensitive Ca^{2+} entry following PKA activation involves L-type calcium channels but not modulated selectivity of sodium channels [141, 142]. Later, TTX sensitive calcium currents were reported from multiple animal models strengthening the evidences against the slip mode conductance hypothesis [71, 143-145]. Thus, the slip mode conductance hypothesis has been abandoned. Nevertheless, there is a possibility that this mode of Ca^{2+} entry might need to be revisited. It has been known for a long time that the selectivity of sodium channels is determined by a small number of amino acids. In the same time, single mutation in the selectivity filter can render the channel permeable to Ca^{2+} [146-149]. Knowing that various sodium channel mutations [5, 83, 97, 99, 103, 150-152] exert diverse impact on the electrophysiology and are associated with deteriorating effects on ionic homeostasis of cardiac myocytes it is plausible that some mutation might involve altered ion selectivity.

4.3.3. Interaction between $I_{Na,L}$ and Sodium/Calcium Exchanger

The function of NCX in cardiac myocytes is highly complex [124, 153-156]. NCX transports Ca^{2+} into or out of the cell depending on the membrane voltage and the gradients of Na and Ca^{2+} across the membrane. at the beginning of systole when the membrane is depolarized, the driving force for the Na^+/Ca^{2+} exchanger puts NCX at the reverse mode. During this time the NCX transports Ca^{2+} into the cytoplasm while removing Na^+ (reverse mode) [134, 155]. Starting at the late systole and throughout the diastole, NCX operates in the forward mode to remove Ca^{2+} from cytoplasm in exchange with Na^+ entry () [134, 155]. This function is crucial for restoring diastolic Ca^{2+} level and for long term calcium homeostasis. However, increased Na^+ concentration in the cytoplasm shifts the Na^+/Ca^{2+} equilibrium to reduce Ca^{2+} removal and facilitate calcium entry, resulting in Ca^{2+} overload. The consequence is analogue to the digitalis induced Ca^{2+} loading leading to elevated cytosolic Ca^{2+} level [154, 157].

5. MODULATION OF LATE SODIUM CURRENT

The heart adapts to changing conditions, such as physical activity, environmental stress or emotional state. This adaptation requires moment-to-moment fine tuning of ion channels and transporters, including sodium channels. The late sodium current is known to be modulated by several physiologic and pathologic factors.

5.1. The Complex Modulation of $I_{Na,L}$ by Cytosolic Ca^{2+}

Ca^{2+} couples electric signal to contraction machinery in cardiac myocytes and provides an important feedback signal to ion channels and pumps of sarcolemma. Voltage gated Na^+ channels are known to be regulated by Ca^{2+}, calmodulin (CaM), Ca^{2+}-CaM dependent protein kinase (CaMK) and protein kinase C (PKC). These molecules in the signaling cascade modulate $I_{Na,L}$ individually and cooperatively [158-162]. Though volume of research data on Ca^{2+}-CaM–CaMK dependent regulation of $I_{Na,L}$, accumulates rapidly, the complex mechanism of this function is still not understood due to confliction observations. In spite of contradictory data on the individual elements, there is a consensus on that Ca^{2+}-CaM–CaMK signaling facilitates cardiac sodium current, especially the late component [23, 158, 163]. The Ca^{2+} dependent modulation (both direct and indirect) modifies the inactivation of sodium channels. The sodium channel inactivation is a very complex process, involving cooperation of multiple distant regions (C-terminus, cytoplasmic linker between domain II and IV, and S4-S5 linkers of domains III & IV) [164]. Ca^{2+} or CaM binding to this region is known to induce a small (5-10 mV) shift in the steady-state inactivation (SSI) curve. Because of the steepness of the function and the vicinity of resting membrane potential to the midpoint, relatively small changes in voltage sensitivity results in significant impact on the availability of sodium channels thus in turn on membrane conductance. Since the membrane potential approaches the sodium equilibrium potential when sodium conductivity is maximal, we can assume that any change in sodium channel availability has stronger impact on the late than that of transient phase of sodium current. There are multiple Ca^{2+} and CaM binding locations identified between c-terminus and domain III allowing highly complex regulation of channel function. Because of this complexity, mutations in the Ca^{2+} sensing region or pathologic conditions altering the Ca^{2+} sensitivity may lead to diverse functional disturbances.

5.1.1. Sodium Channel and Ca^{2+}

The most ambiguous part of Ca^{2+} - CaM – CaMK dependent regulation of $I_{Na,L}$ is that whether Ca^{2+} can modulate cardiac sodium channel directly. The question was addressed by Wingo *et al*. in 2004 who proposed that Ca^{2+} binds directly to a dedicated motif located close to c-terminus and modulates Na^+ channel function [165]. This conclusion was supported by several lines of experimental data. First, a calcium binding motif (referred as EF hand) known from other Ca^{2+} regulated proteins was identified between domain IV and the CaM binding site in the cardiac sodium channel (Fig. **2**). Second, using NMR spectroscopy it was demonstrated that Ca^{2+} effectively binds to this EF hand. Third, voltage clamp experiments revealed that steady-state inactivation is shifted toward positive voltages in high cytosolic Ca^{2+} even in the presence of a CaM inhibitory peptide. Furthermore, mutations in the EF hand prevented both Ca^{2+} binding to EF motif and high Ca^{2+} induced shift in steady-state inactivation. These consistent observations led the authors to the conclusion that Ca^{2+} exerts direct regulatory effect on sodium channel. However, several observations from other groups suggested that CaM is essential to mediate Ca^{2+} effect whereas Ca^{2+} does not regulate sodium channel directly [166, 167]. The most important critique against the data from Wingo *et al*. was that the inhibitory peptide they used might not effectively prevent binding of CaM to sodium channels [164]. To resolve the conflicting data reported by many independent experimentalists a new model was proposed by Shah *et al* [168]. According to this model, the sodium channel inactivation is modulated by the interaction between Ca^{2+} binding EF hand and CaM binding IQ motif. In diastolic conditions, CaM binds to IQ motif of the c-terminus. When cytosolic Ca^{2+} concentration is high, CaM binds calcium which reduces its affinity to IQ segment. In the next step Ca/CaM detaches from IQ motif enabling it to interact with the EF hand, which is the critical step in this model: as it is proposed, binging of IQ motif to EF hand increases the calcium affinity of the EF hand by three order of magnitude. Later, Biswas and co-workers confirmed the direct Ca^{2+} regulation of sodium channels, but using truncated mutants they have shown that the IQ motif is not essential for the direct Ca^{2+} regulatory effect [169]. They also proposed that CaM-mediated regulation is latent in cardiac sodium channel unless it is unmasked by mutations of the EF hand, or by extremely low Ca^{2+} concnetration in cytoplasm.

5.1.2. Calmodulin

Calmodulin (CaM) is a ubiquitous calcium sensing protein that mediates Ca^{2+} effects in various types of cells, including cardiac myocytes [166, 167]. CaM was shown to interact with the IQ motif of sodium channel and regulate gating mechanism [164, 166, 170]. The three dimensional configuration of CaM resembles a dumbbell; the C and N-terminus of the protein forms two globular structures (referred as C-lobe and N-lobe respectively) with two calcium binding regions interconnected with a short flexible shaft. Each lobe can bind two Ca^{2+} ions. At physiologically relevant Ca^{2+} concentrations the Ca^{2+}/CaM complex forms a bridge between IQ motif on C-terminus and the DIII-IV linker region [171]. This linker region is considered the inactivation gate of sodium channel [172]. When Ca^{2+} concentration is low and CaM is free of Ca^{2+} (apo-CaM), the C-lobe is bound to the IQ motif of C-terminus. In this configuration, the N-lobe does not interact with the DIII-IV region and inactivation is not affected [168, 171, 173]. When Ca^{2+} concentration is

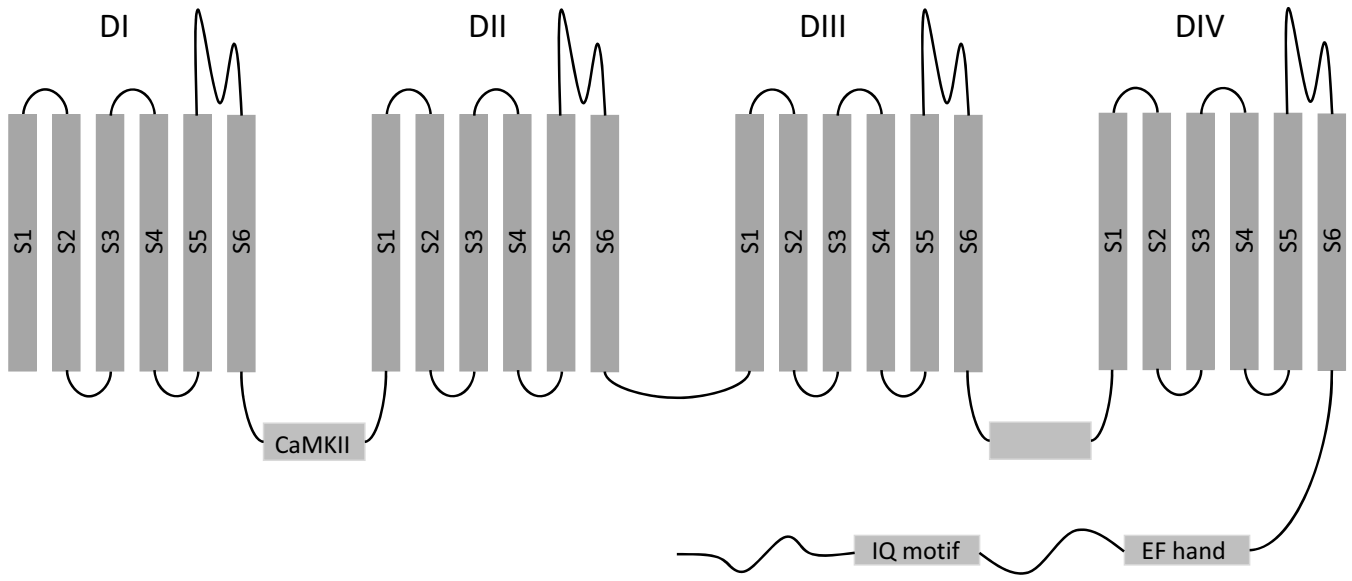

Fig. (2). Schematic representation of the structure of the α-subunit of cardiac sodium channel

Each domain (DI-DIV) consists of six transmembrane segments (S1-S6) interconnected by intracellular and extracellular loops. The intracellular loop between DI-DII is the target region for CaMKII, DIII-DIV loop serves as inactivation gate and c-terminus is the Ca^{2+} and CaM sensor.

elevated, Ca^{2+}/CaM complex (holo-CaM) is formed and its affinity for the IQ motif is reduced by an order of magnitude [168]. There is a switch between C and N-lobes, and holo-CaM binds to the IQ motif through N-lobe. According to the model proposed by Sarhan *et al*, C-lobe can interact with the DIII-IV linker in this configuration and the interaction results in a shift in SSI curve to depolarizing direction. These observations indicate that the interaction between the C-lobe of holo-CaM and DIII-IV linker is responsible for the altered voltage sensitivity of inactivation [171]. Nevertheless, the holo-CaM/DIII-IV interaction is not the only possible mechanism behind high Ca^{2+} induce rightward shift of steady-state inactivation, because the Ca^{2+} sensitivity is retained in the sodium channels even after IQ motif deletion. [169]. As discussed above, Ca^{2+} can bind to the EF-hand of C-terminus to alter the voltage sensitivity of inactivation. Parallel to the direct regulation of sodium channel, CaM activates Calmodulin Kinase that further modulates the channel kinetics [174].

5.2. Protein Kinases

The α subunit of cardiac sodium channel contains multiple phosphorylation sites located in the N-terminus and the first and third intracellular linker loop [175-178]. Phosphorylation of the channel may modulate gating kinetics to change the magnitude of $I_{Na,L}$.

5.2.1. Calmodulin Kinase

Cardiac calmodulin kinase is a serine/threonine kinase involved in a multitude of cellular function in vide variety of cells including cardiac myocytes. The enzyme associates with and phosphorylates the α subunit of channel protein to alter the gating kinetics [179]. Cardiac myocytes express two predominant isoforms of calmodulin kinase type II (CaMKII): the nuclear (δ_B) and the cytoplasmic (δ_C) isoform. Sodium channels are regulated by the cytoplasmic isoform [158, 180, 181]. It is well established that CaMKII phosphorylates sodium channels at multiple sites (S571, S483/S484, S516, T594) in the first intracellular linker loop, resulting in complex effects that lead to increase of $I_{Na,L}$ [170, 179, 182]. Generally, upregulation of CaMKII was shown to induce a negative shift in steady-state inactivation, to enhance the slow or intermediate inactivation, and slowed recovery from inactivation. These effects individually and collectively may lead to gain- and loss-of function of the sodium current, contributing to pathologic conditions like Brugada syndrome [182, 183]. Furthermore, CaMKII was shown to augment $I_{Na,L}$ and slow its decay in both normal an failing dog hearts [163].

While substantial species-dependent differences were reported on the impact of CaMKII induced phosphorylation on sodium channel gating, the overall effect is to increase the late sodium current, and conversely inhibition of the enzyme reduces $I_{Na,L}$. Wagner and co-workers reported negative shift of steady-state inactivation in rabbit cardiac myocytes following overexpression of CaMKII [179]. This observation was confirmed in expression system using HEK293 cells by Ashpole *et al* and Koval *et al* [182, 184]. In contrast, when Aiba and co-workers used freshly isolated guinea pig ventricular myocytes and CaMKII was directly added to the pipette solution, they observed a positive shift in steady-state inactivation [170]. Data regarding the activation of current are also inconsistent. Young and Caldwell reported a hyperpolarizing shift in the voltage dependence of activation [185], whereas no effect was seen by others [170, 179, 182, 186]. Aiba *et al* also reported increased peak amplitude for the transient phase of sodium current [170], while others reported no change in this parameter [179, 182, 184]. There is little information on inactivation of the transient phase of I_{Na}. Wagner at al. observed significant deceleration of I_{Na} decay in the transient phase, but Aiba *et al*. observed no change [170]. Nevertheless, the majority of reports agree that CaMKII enhances the fraction of channels undergoing intermediate or slow inactivation. Consequently, upregulation of CaMKII facilitates $I_{Na,L}$ and this is reversible with CaMKII inhibitors. A recent study by Horvath *et al*. used ^{self}AP-clamp to record the $I_{Na,L}$ during the action potential under physiological condition, and clearly show that the magnitude of $I_{Na,L}$ during the action potential plateau phase is reduced by CaMKII inhibition [18]. The link between increased CaMKII activity and facilitated $I_{Na,L}$ is confirmed in both healthy and diseased myocardium by others [162, 163, 187].

5.2.2. Protein kinase A (PKA)

PKA is the mediator of ß-catecholamine signalization and key regulator of multiple functions in cardiac cells. The enzyme is

shown to facilitate sodium channel trafficking to sarcolemma thus increasing the $I_{Na,T}$ [188, 189]. However, there are several conflicting observations regarding the PKA dependent modulation on sodium channel gating and the physiologic function of PKA remains controversial [170, 183]. Tateyama *et al.* addressed the PKA modulation of $I_{Na,L}$ in expression model comparing wild type channels and three disease linked mutants. According to their observations, $I_{Na,L}$ is insensitive to PKA-dependent phosphorylation in wild type channels whereas one of the pathologic mutant displayed enhanced $I_{Na,L}$ following PKA activation [190].

5.2.3. Protein kinase C (PKC)

At least seven members of PKC family is identified in mammalian myocardium [191]. Classic isoforms are activated by Ca^{2+}, but several isoforms expressed in the heart are known to be insensitive to Ca^{2+} [161]. Some isoforms require diacylglycerol and/or phospholipid for activation, thus activated through the same pathway as phospholipase C. The expression level of the isoforms shows species-specific differences therefore interpretation of data must be done with caution. Further complications arise from the overlap in Ca^{2+} activation with CaMKII.

The serine residuum (rodent: S1505, human: S1503) phosphorylated by PKC is located in the third intracellular loop of cardiac sodium channel known to play key role in the inactivation of I_{Na} [177, 183]. In expression system, PKC activation resulted in negative shift in steady state inactivation and voltage dependent decrease of peak amplitude. Single-channel data reported by Qu *et al.* showed that the probability of early ($t<5$ ms) and late ($t>10$ ms) channel openings were reduced when studied in Xenopus expression model [192]. In contrast, when Ma *et al.* studied the impact of elevated cytosolic Ca^{2+} on $I_{Na,L}$ in isolated rabbit ventricular cardiac myocytes, they observed PKC dependent facilitation of the current [162]. The conflicting results could be explained by the different experimental models. In the expression system used by Qu *et al.* only α-subunit was expressed, whereas in the isolated cardiac myocytes used by Ma *et al.* $I_{Na,L}$ was measured in intact channels. Recently, Ashpole *et al*. proposed that regulatory effects of CaMKII induced α-subunit phosphorylation cannot manifest on the cardiac sodium channel without the presence of additional protein, like ß-subunit [182]. It is possible that, PKC phosphorylation cannot modulate the channel gating in the absence of ß-subunit.

5.2.4. Serum- and Glucocorticoid-Inducible Kinases

Originally, serum- and glucocorticoid-responsive kinases (SGKs) were cloned in embryonic mammalian hearts and tumor cells, but later the enzyme was identified in virtually all tissues tested [193-195]. Until now, three isoforms (SGK1, SGK2 and SGK3) were characterized from different tissues. SGK1 and SGK3 are the dominant forms in heart, while the expression of SGK2 is restricted [196]. SGKs are serine-threonine kinases showing high homology to Akt and share common downstream substrate with Akt [193, 197]. The regulation of SGKs is fast; the activation and degradation of SGK can occur in less than a half hour [194, 195]. The enzyme is activated by several factors including insulin, insulin-like growth factor, serum, glucocorticoids and oxidative or mechanical stress [193, 196]. Upregulation of SGKs was observed in diverse pathologic conditions, like wound healing, diabetic nephropathy, liver cirrhosis, cardiac fibrosis and heart failure [194, 195, 198]. SGKs were demonstrated to inhibit apoptosis and enhance hypertrophic response in cultured cardiac myocytes [193].

SCN5A has been shown to be stimulated by SGKs in multiple ways [198, 199]. First, the kinase modulates the gating kinetics of the sodium channel. In Xenopus expression system SGK was demonstrated to shift the inactivation curve to more positive voltages and the activation curve to more negative direction resulting in broadening of the window current [199]. In mouse cardiac myocytes SGK shifted both activation and inactivation curves toward negative voltages resulting in a negative shift of the crossing point [198]. Second, upregulation of SGK increases sodium channel availability and thus the current density [198, 199]. The mechanism involves phosphorylation and reduced binding of ubiquitin ligase Nedd4-2 to PY motif of SCN5A. Previously, cortisol was shown to regulate the cardiac SCN expression in fetal sheep myocardium [200]. These observations raise the possibility that SGKs can be potentially important candidate for modulating $I_{Na,L}$. Surprisingly, this possibility has not been well studied. Das *et al*. reported substantial increase of $I_{Na,L}$ in ventricular myocytes of transgenic mice with constitutively active SGK1. The increased $I_{Na,L}$ coincided with lengthened AP, more frequent afterdepolarizations and increased propensity for ventricular arrhythmias. Ranolazine has been shown to normalize the AP duration and suppress both afterdepolarizations and arrhythmias [198].

5.3. Cellular Metabolism

Metabolic activity of cardiac myocytes adapts to the momentary changes in the cardiac output, blood pressure, autonomic regulation determined by varying environment, physical activity or even emotional state. Cardiac sodium channels has been shown sensitive to the metabolic state of the cell and modulated by pH, oxygen or metabolites. During myocardial hypoxia extracellular pH can drop as low as 6.0 [201], and cardiac sodium current is known to be modulated by these substantial increase in the proton concentration [70, 202-205]. There is a consensus on that acidosis reduces the magnitude and the decay of the $I_{Na,T}$. Furthermore, positive shift in voltage dependency of activation and inactivation was observed in Xenopus expression system [203-205]. Additionally, Jones *et al*. demonstrated an increase in the window current and deceleration of the time constant of slow inactivation in Xenopus oocytes. Based on these data they predicted AP lengthening at low pH in a computer model [203]. Murphy *et al*. reported depolarizing shift in voltage dependency of activation, but not in the steady-state inactivation in freshly isolated canine ventricular myocytes [70, 202]. In agreement with Jones *et al*., they observed the prolongation of AP at low pH, but they found that $I_{Na,L}$ was reduced in both endocardial and epicardial myocytes [70].

Acute and chronic hypoxia is known to induce electric disturbances in myocardium leading to arrhythmia. Several studies addressed the effect of hypoxia on the late sodium current, and all observations employing wide variety of experimental models consistently showed that hypoxia increases $I_{Na,L}$ [11, 206-210]. Wang *et al*. studied the mechanism of hypoxia induced $I_{Na,L}$ facilitation [206]. Recording single channel current they found increased burst mode activity following 15 minutes hypoxia that may explain the increased persistent sodium current. They also reported hyperpolarizing shift in the steady-state inactivation curve resulting in significant reduction of $I_{Na,T}$ and probably attenuating hypoxia induced facilitation of $I_{Na,L}$ due to reduced window current. Interestingly, Wang *et al*. found that hypoxia shortens AP duration in spite of increased $I_{Na,L}$ which indicate that other hypoxia sensitive ion channel(s) also contribute to reshaping AP in cardiac cells.

Hydrogen peroxide and free radicals were demonstrated to stimulate $I_{Na,L}$ by several teams [127, 211-213]. In accordance with these observations, specific $I_{Na,L}$ inhibitor ranolazine or TTX attenuated the AP lengthening effect of H_2O_2 [213]. However, Erickson *et al*. showed that free radicals can directly activate CaMKII [214]; therefore CaMKII might be involved in $I_{Na,L}$ facilitation in the presence of free radicals.

$I_{Na,L}$ is modulated by wide variety of metabolites and second messengers. Poly-unsaturated fatty acids, like docosahexaenoic and eicosapentaenoic acids (DHA, EPA) were shown to substantially reduce both transient and late phase of I_{Na} [215]. The reduction develops from hyperpolarizing shift in the inactivation and activation curves decreasing the window current. An ischemic metabolite, lysophosphatidylcholine was also demonstrated to reduce $I_{Na,T}$, but effects on $I_{Na,L}$ has not been addressed in those studies [12, 216].

Nitric oxide (NO) was found to facilitate $I_{Na,L}$ by Ahern and coworkers fifteen years ago; they proposed that nitrosylation of sodium channels within plasma membrane modify the gating of cardiac sodium channel [217]. Since then the mechanism has been confirmed by Cheng *et al*. demonstrating that caveolin-3 mediates sodium channel nitrosylation [218].

5.4. Ubiquitylation

The number of sodium channels at the sarcolemma (therefore sodium current density) is determined by a delicate balance between expression/translocation and internalization/degradation of channel proteins. Covalent attachment of ubiquitin to lysine residues situated in specific position within the substrate proteins was shown to label membrane proteins, including cardiac sodium channels for internalization and degradation [219-223]. Ubiquitin is a small peptide present in all eukaryotic cells. Ubiquitylation is a multistep process achieved by specific enzymes responsible for activation, conjugation and ligation. Cardiac sodium channels are specifically recognized and ubiquitylated by Nedd4-2 an ubiquitin-protein ligase resulting in reduction of channel density in the cell membrane, and thus downregulate I_{Na}. Furthermore, Nedd4-2 labels SGKs too decreasing the steady state level of the enzyme resulting in reduced phosphorylation of cardiac sodium channels. Interestingly, activation of Nedd4-2 requires phosphorylation by SGK1, thus SGK1 forms a self-limiting regulatory loop with Nedd4-2 [195].

5.5. Mechanical Stress

Myocardial wall tension is subjected to moment-to-moment changes during cardiac cycle, and ion channels embedded in the cell membrane experience varying mechanical stress. It is well established that cardiac sodium channels respond to mechanical stress with altered gating kinetics [50, 224]. Beyder *et al*. investigated the mechanosensitivity of Na_v 1.5 in expression model using cell-attached patch clamp configuration and characterized the stretch-induced modulation of I_{Na} [50]. Increased stretch of the patch resulted in a negative shift in both the inactivation and activation curves and decelerated recovery from inactivation. Interestingly, the membrane stress increased the availability of channels under the patch, leading to increased peak current. Recently, the same group confirmed these observations on freshly isolated mouse ventricular cells [225]. Moreover, in the same publication authors demonstrated that ranolazine inhibits the mechanosensitivity of cardiac sodium channels in a dose-dependent manner. Further supporting evidences on inhibitory effect of Ranolazine on mechanosensitivity of Na_v 1.5 has been obtained in cultured atrial myocytes by the same team [226]. Ranolazine is antiarrhythmic drug known to target cardiac sodium channels and inhibiting the late current $I_{Na,L}$ with high selectivity over the $I_{Na,T}$ [44, 52, 128, 227, 228]. Considering that myocardial wall stretch is known to play key role in arrhythmogenesis [229-231] these data may help to establish a new therapeutic strategy in antiarrhythmic pharmacology. Currently, pharmacological reduction of preload with diuretics and vasodilators represents the only therapeutic approach to reduce wall stress and prevent disease progression in arrhythmogenic right ventricular cardiomyopathy [232, 233]. Reducing mechanical sensitivity of the electric system in cardiac myocytes may present a new therapeutic strategy.

6. THE LATE SODIUM CURRENT IN HEART DISEASES

It is now well established that the upregulation of $I_{Na,L}$ results in pathologic cardiac function including contractile dysfunction, arrhythmia and structural heart disease [5, 6, 42, 45, 58, 79, 102]. There are several conditions (mutation, hypoxia, ischemia, carbon monoxide, CaMKII or angiotensin II activation, etc.) known to facilitate $I_{Na,L}$ and leading to cardiac dysfunction [6].

There are two possible mechanisms to facilitate $I_{Na,L}$: increasing the channel density and altering channel gating. Increased expression of non-cardiac sodium channel isoforms were observed in postinfarction remodeled myocardium and pressure overload model [40, 234]. In the same time, altered channel gating was proposed as possible mechanism for increased $I_{Na,L}$ in various diseased models [11, 38, 162, 206, 209, 235]. It is possible that facilitation of $I_{Na,L}$ may not fully result from increased expression of non-cardiac channels in chronic heart disease. Myocardial hypoxia and increased expression is often present in different structural and functional heart diseases [180, 181]. Therefore current experimental data are insufficient to reliably isolate the consequences of altered subunit expression from changed gating mechanism in facilitation of $I_{Na,L}$ in pathologic states. Interestingly, increased $I_{Na,L}$ was reported in atrial fibrillation with reduced expression of Na_v 1.5 and decreased $I_{Na,T}$ [236].

The impact of the sustained sodium current on cardiac function is complex. The current flowing through sodium channels during plateau is very small relative to the currents causing either the upstroke or terminal repolarization of AP. However, to understand the functional relevance of $I_{Na,L}$ in cardiac function it is important to understand that (1) other currents flowing under the plateau have very low magnitude as well, therefore the contribution of $I_{Na,L}$ to the profile of plateau is significant. Furthermore, (2) the amount of Na^+ entering into the cell significantly contributes to the intracellular sodium content of cardiac myocytes. The transient phase of I_{Na} is short with high peak; the majority (90-95%) of sodium ions passes the membrane in less than 5 ms. In contrast to that, the magnitude of the sustained part is less than 1% of the peak lasting for several hundred ms. Thus, in spite of the remarkable difference in the magnitude, the amount of sodium entering into the cardiac myocytes during the transient and sustained phase of I_{Na} are comparable [237, 238].

6.1. $I_{Na,L}$ and the Ion Homeostasis of Cardiac Cells

Plateau sodium current adds substantial amount of sodium to the total entry during electric cycle. When $I_{Na,L}$ is enhanced, Na^+ influx can be increased several fold resulting in increased cytosolic sodium concentration. Sodium is extruded from the cells by Na^+/K^+-ATPase (NKA) with stoichiometry of 3/2 using one ATP molecule in each pump cycle. The K_D for ATP and potassium are 1-2 mM and 80-150 μM respectively; therefore, ATP or extracellular K^+ concentration is not a limiting factor for NKA activity, because intracellular ATP and extracellular K^+ concentrations are significantly higher than these values [124]. In contrast to these, the K_D for Na^+ is in the range of 10-20 mM and the intracellular Na^+ concentration falls to the range of 5-15 mM resulting in high sodium sensitivity for NKA. Thus, increasing cytosolic Na^+ concentration stimulates NKA and increases ATP catabolism. Considering that, $I_{Na,L}$ upregulation often coincide with ischemic/hypoxic conditions, the increased ATP utilization can worsen the energetic state of cardiac myocytes depleting the ATP pools of the cell. Besides, experimental observations indicate that, in spite of the facilitation, NKA cannot keep cytosolic sodium concentration in the normal range and increased $I_{Na,L}$ results in elevated cytosolic Na^+ concentration [126, 127].

Elevated cytosolic sodium concentration shifts the equilibrium potential for Na^+/Ca^{2+} exchanger facilitating reverse mode and inhibiting forward mode; hence, some of the extra sodium entered is converted to calcium [72, 124, 154, 239, 240]. Ca^{2+} is the key regulator of the majority of functions in cardiac myocytes, including metabolism, electric activity, contractility as well as apoptosis [158, 180, 181, 240-243]. Elevated cytosolic calcium leads to Ca^{2+} overload in sarcoplasmic reticulum resulting in contractile dysfunction and increased risk for arrhythmia [52, 244-248].

6.2. Role of $I_{Na,L}$ in Arrhythmogenesis

Acquired or inherited increase of $I_{Na,L}$ is associated with enhanced risk for cardiac arrhythmia and inhibition of $I_{Na,L}$ was demonstrated to prevent or abolish arrhythmic electric activity of the heart [1, 3, 5, 6, 42, 58, 128, 245, 246]. There are multiple mechanisms $I_{Na,L}$ might lead to manifest arrhythmic activity.

First, increase of any inward current – like $I_{Na,L}$ – during the plateau can cause AP prolongation, increasing the risk for early afterdepolarizations (EAD). EADs are documented to occur more frequently at long AP duration resulted from either increased inward or decreased outward currents. EADS are slow membrane potential oscillations due to reactivation of inward currents during phase two and three of AP and implicated in triggered arrhythmias [249, 250]. The possible candidates for the reactivating currents are $I_{Ca,L}$, $I_{Na,L}$, and I_{NCX}. I has been postulated that augmentation of $I_{Ca,L}$ or $I_{Na,L}$ occurs by window mechanism [9, 98, 138]. Calcium overload was documented also to promote the generation of EAD but the mechanism is not completely understood [251, 252]. However, it has been proposed that spontaneous calcium release from sarcoplasmic reticulum might facilitate I_{NCX} and induce membrane oscillations [138, 249, 251, 252]. Horvath and his co-workers recently investigated the role of $I_{Na,L}$ in generation of EAD [18]. They showed that facilitation of $I_{Na,L}$ by Anemone toxin II prolonged APD and induced Ca^{2+} oscillations that led to EADs, but these arrhythmogenic activities were eliminated by buffering cytosolic Ca^{2+} with BAPTA. From these observations they concluded that $I_{Na,L}$ may contribute to AP prolongation that favors the generation of EAD, but membrane oscillation arise from augmentation of I_{NCX} due to cytosolic calcium oscillations.

Second, upregulation of $I_{Na,L}$ was shown to facilitate generation of spontaneous depolarizations developing at resting membrane potential (between two APs) and referred as delayed afterdepolarizations (DAD) [39, 253]. There is a consensus opinion on that DADs arise from spontaneous calcium release from the sarcoplasmic reticulum that facilitate I_{NCX}, a similar mechanism discussed previously with regard to EADs [254-257]. In this sense, $I_{Na,L}$ does not provide the depolarizing power for the depolarization, but inducing calcium overload 'set the stage' for spontaneous cytoplasmic Ca^{2+} oscillations [6].

Third, an increase of $I_{Na,L}$ is known to facilitate beat to beat variability and regional inhomogeneity of AP duration [8, 86, 212, 235, 258]. Increased beat to beat variability results from reduced repolarization reserve and makes the heart more vulnerable to potentially proarrhythmic prolongation of the APD [259]. Regional differences in AP duration are generally attributed to asymmetrical distribution of various ion channels [107, 260-265]. The transmural heterogeneity of $I_{Na,L}$ was discussed previously. Increase in both beat to beat variability and transmural heterogeneity may result in increased prevalence of cardiac arrhythmias due to increased dispersion under certain (usually pathological) conditions [266, 267].

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia [268, 269]. It is known to cause electric remodeling of the atrial myocardium that leads to reduced L-type calcium current, potas-

Table I. List of pharmacons reported to inhibit $I_{Na,L}$

Name	EC_{50}	Effective cc.	Selectivity
AZD1305	4.3 μM [300]		EC_{50} for $I_{Na,T}$: 66 μM [300]
F15845	5.3 μM [301]		
GS967	0.13 μM [128]		$I_{Na,T}$: 7.5% inhibition at 10 μM [128]
KC 12291	9.6 μM [302]		25% I_{K1} inhibition at 10 μM; 42% I_{to} inhibition at 10 μM [303]
R 56865	200 nM [304]		Binds to α_1-adrenoceptors, 5-HT receptors, DHP receptors with K_i between 20-340 nM [305]
RSD1235 (Vernakalant)	31 μM [306]	30 nM [307]	EC_{50} for Kv1.5, Kv4.2 and Kv4.3: between 10-40 μM; I_{K1}: 1 mM; $I_{Ca,L}$: 220 μM [306]
Amiodarone	6.7 μM [283]		EC_{50} for $I_{Na,T}$: 87 μM [283]; I_{Kr}: 2.8 μM [308]. Inhibits I_{K1} and I_{Ks} in concentration higher than 10 μM [309, 310]
Flecainide	3.4 μM [128]		EC_{50} for $I_{Na,T}$: 84 μM [128]
Mexiletine	18 μM [311]		EC_{50} for $I_{Na,T}$: 35 μM; No effect on $I_{Ca,L}$ up to 100 μM [311]
Ranolazine	17 μM [128] 6 μM [227]		EC_{50} for $I_{Na,T}$: 1329 μM [128]; EC_{50} for I_{Kr} : 12 μM, I_{NCX} : 91 μM, $I_{Ca,L}$: 50 μM [227]
Resveratrol	34 μM [312]		
Sophocarpine		30 μM [313] 20-80 μM [246]	Inhibits I_{NCX} in concentrations higher than 20 μM [246]
Wenxin Keli	4 μM [299]		EC_{50} for $I_{Na,T}$: 11 μM [299]

sium currents and AP duration [270, 271]. Interestingly, $I_{Na,T}$ was found to be reduced while $I_{Na,L}$ was facilitated in AF patients [236].

6.3. $I_{Na,L}$ and Structural Heart Disease

The most argued cardiac disorder linked to $I_{Na,L}$ is dilated cardiomyopathy (DCM) a progressive structural heart disease characterized by reduced myocardial force generation and enlarged chambers. In spite of the increasing volume of evidence that links *SCN5A* mutations to DCM, the mechanism how a defective ion channel function leads to structural disease remains unclear. The first observations that associated DCM to *SCN5A* mutation was published in 2004 and 2005 from two different groups [101, 272]. The strikingly new hypothesis that sodium channel gene mutation may lead to structural heart disease was challenged by Groenewegen & Wilde suggesting the role of another gene, different from *SCN5A* in DCM phenotype [273]. In the following years new *SCN5A* mutations were identified in DCM patients providing further evidence that sodium chanellopathy can be associated with structural heart disease [103, 274]. In 2012 Gosselin-Badaroudine and his coworkers have shown that the mutation in these sodium channels resulted in a proton leak through an alternative pore not related to the Na^+ path [275]. They proposed that acidification of cardiac myocytes may cause the DCM phenotype of these patients.

7. THE LATE SODIUM CURRENT AS THERAPEUTIC TARGET

Several compounds are known to increase or inhibit $I_{Na,L}$, and a few of them are employed in clinical practice as antiarrhythmic drug. Compounds known to facilitate late sodium current are used exclusively as pharmacological tool for research because they promote arrhythmogenesis that prevents their clinical application [1, 2]. The most frequently used $I_{Na,L}$ activators seen in research papers are Veratridine and Sea Anemone Toxin (ATX-II); ATX-II is more specific than Veratridin [18, 126, 128]. Other activators like ouabaine or Pyrethroids are also used for research purposes but held more 'dirty' [6, 126].

Pharmacological suppression of plateau sodium current was shown beneficial to reduce contractile dysfunction and arrhythmic activity in several pathologic model [46, 225, 245, 276-279]. Since $I_{Na,L}$ is the non-inactivating component of $I_{Na,T}$, it is inhibited by sodium channel blockers including quinidine, mexiletine or local anesthetics like lidocaine. It is very likely that beneficial effects of traditional Class I sodium channel blockers are exerted via $I_{Na,L}$ inhibition. However, Class I drugs display strong proarrhythmic effects and increase mortality; this led to the opinion that treatment of arrhythmias with sodium channel blockers is harmful. Thus, research has shifted toward selective $I_{Na,L}$ blockers with no inhibitory effect on $I_{Na,T}$. Some of the classic sodium channel inhibitors including lidocaine, mexiletine or flecainide (Fig. **3**) display 5-10-fold $I_{Na,L}$ selectivity over $I_{Na,T}$ (see Table **1**), but these drugs significantly suppress conductivity in the therapeutic range promoting reentry type arrhythmia [280-282]. Mixed ion channel blocker amiodarone has outstanding $I_{Na,L}/I_{Na,T}$ selectivity amongst traditional antiarrhythmic drugs [283], but chronic amiodarone is documented to carry severe side effects preventing its use in long term therapy [284-293].

The first, highly selective $I_{Na,L}$ blocker with no known adverse effects was Ranolazine, an anti-ischemic, antianginal drug [278,

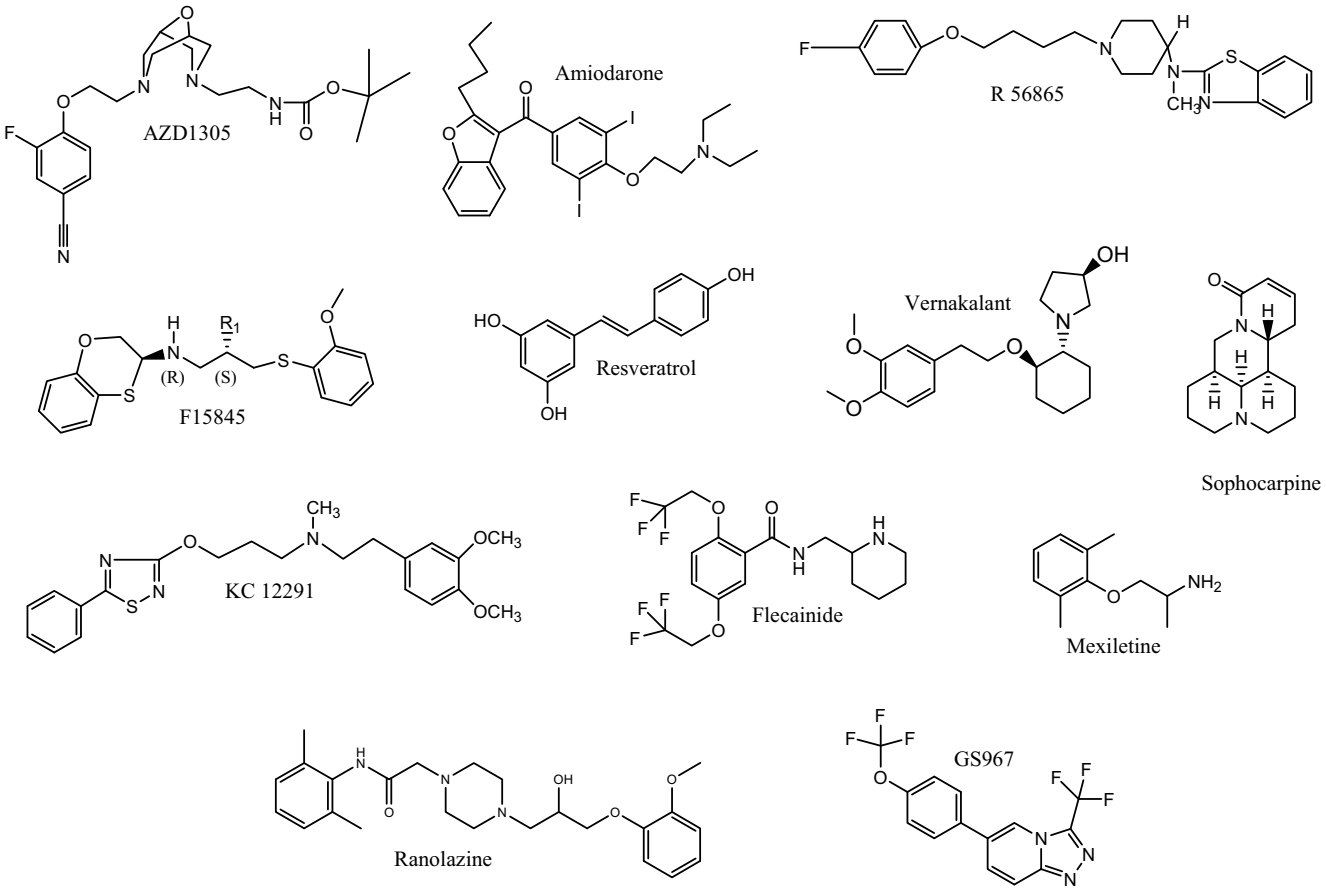

Fig. (3). Chemical structures of $I_{Na,L}$ inhibitors.

279]. Ranolazine (Fig. **3**) effectively inhibits late sodium current with 17 and 1300 μM EC_{50} for $I_{Na,L}$ and $I_{Na,T}$ respectively [128]. Apart from the primary $I_{Na,L}$ inhibitory effect, Ranolazine was also demonstrated to decrease calcium overload, improve mechanical dysfunction and reduce mechanosensitivity of sodium channel [225, 226, 245]. However, Ranolazine reduces I_{Kr}, I_{NCX} and $I_{Ca,L}$ with EC_{50} value between 12-90 μM and blocks catecholamine receptors too [294, 295]. The success of Ranolazine stimulated research to develop highly selective $I_{Na,L}$ blockers with less side effects (see Table **1**).

Recently a new promising molecule, compound GS967 (Fig. **3**) was shown to attenuate ischemia and methoxamine-clofilium induced arrhythmia in rabbit. GS967 is more potent and effective inhibitor for $I_{Na,L}$ than Ranolazine with higher EC_{50} for I_{Kr} [128].

Sodium channels show higher affinity for sodium channel blockers in activated or inactivated, but not in closed state [296]. Diastolic phase is shortened in AF which favors drug binding to the channel resulting in substantial selectivity for the drug to fibrillating atrium over ventricle. When heart returns to sinus rhythm, diastolic period lengthens and the drug dissociates from the channel removing the inhibition. Furthermore, Ranolazine was shown to inhibit $I_{Na,L}$ more effectively in AF than in sinus rhythm myocytes [236]. Though, data from large scale double-blind, placebo controlled clinical studies are not available, preliminary clinical studies with AF patients showed that Ranolazin treatment appeared more effective in treating AF than that of standard amiodarone therapy [4, 297, 298].

An interesting work was published in 2013 by an international team in PACE [299]. Xue at al. studied the effect of a Chinese herb extract, Wenxin Keli on ventricular arrhythmias in rabbit model. Wenxin Keli is used in traditional medicine as treatment for angina and various arrhythmias. Authors showed in their paper that Wenxin Keli suppresses afterdepolarizations and inhibits $I_{Na,L}$ in dose dependent manner. However, the specific component of the extract responsible for the beneficial effects is not identified.

DISCLOSURES

Non declared.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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