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 last decade. The first reports on the sustained component of voltage activated sodium current dates back to the early seventies, but early observations interpreted this tiny current as a product of a few channels that fail to inactivate having neither physiologic nor pathologic implications. $I_{Na,L}$ has emerged recently as a potentially major arrhythmogenic mechanism in various heart diseases attracting the attention of both 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 conclude a series of papers concerned with physiology and regulation of cardiac late sodium current. Focusing on some recent development of the field we discuss here critical evidences implicating $I_{Na,L}$ as a potential target for treating myocardial dysfunction and cardiac arrhythmias.

1. INTRODUCTION

Cardiac arrhythmias are the primary cause 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 remained the most frequently applied medical intervention in controlling arrhythmias.

The tiny sustained part of sodium current termed as late sodium current ($I_{Na,L}$) was out of the focus of research for long time but immediately attained 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. In the same time, inhibition of the currents was demonstrated to prevent or reduce arrhythmic activity in multiple pathologic models.

Exponentially increasing number of research publications and comprehensive reviews [1-6] published in the last few years indicate the great expectation on $I_{Na,L}$ as a new, potential therapeutic target. At the present, one of the greatest limiting factors that delay the progress of the field is the lack of specific $I_{Na,L}$ inhibitors. Developing highly specific $I_{Na,L}$ blockers would facilitate research and could 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]. The concept of $I_{Na,L}$ has been established with this publication. Four years later 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 window mechanism is involved in generation of sustained sodium current and predicted that this current might have large effect on AP duration. Ten years later Kiyosue and Makita conducted a

systematic study on the plateau sodium current in guinea pig ventricular cells [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 both a '*late scattered mode*' and '*burst mode*' known to be responsible for $I_{Na,L}$ (discussed later) and showed the *'normal'* (today: transient) channel activation is followed by late activity in less than 4% of patches. They confirmed *Coraboeuf et al.*'s observation on the AP shortening effect of TTX and suggested $I_{Na,L}$ contributes to regulation of the AP length. The central question in these early years was whether this relatively small current can play a significant role in shaping the AP or not. In the following years $I_{Na,L}$ was shown to be upregulated by hypoxia, free radicals or ischemic metabolites [11-13]. The finding that elevated plateau current was linked to cardiac diseases especially to an increased propensity of arrhythmias gave a huge boost to $I_{Na,L}$ research [14-17]. Recent experimental evidences obtained by modern electrophysiology technique indicated that earlier observations made under equilibrium voltage conditions significantly underestimated the magnitude of $I_{Na,L}$ [18, 19]. When $I_{Na,L}$ is measured by self action potential clamp method, the magnitude of the current is comparable with that of major potassium currents making it a cardinal player in shaping AP [20].

3. The identity of sustained plateau sodium current: one current with multiple mechanisms?

Mammalian cells express several isoforms of voltage-dependent sodium channels distinguishable by their kinetics, unit conductance and drug sensitivity. The dominant isoform in cardiac tissues is referred as $Na_v1.5$ and characterized by relative insensitivity to tetrodotoxin, saxitoxin and μ-conotoxin [21, 22]. Alternative names for this channel encoded by the gene *SCN5A* are *h1* or *skm II* channels. 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. Under resting membrane potential conditions the channel is in non-conductive state, but sufficient depolarization ($V_{1/2}$: -40/-50 mV) activates the channel and shifts it to conductive state [23-25].

3.1. Different 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 opens in less than two milliseconds then inactivates within two ms too [26, 27]. Transition from inactivation to closed state is promoted by repolarization. If membrane remains depolarized the first opening can be followed by several reopening. Maltsev & Undrovinas studying single human cardiac sodium channels observed and modelled three distinct types of activity present in human ventricular myocytes [28]. In *Transient Mode* (TM) the first opening is followed by 5-10 rapid reopening resulted by flip-flops between open and inactive state of the channel (Figure 1). This repetitive activity is terminated within less than 40 ms when channel is absorbed in a second inactive state resulting in rapid decline of ensemble current. The current magnitude drops below 10% of the peak within 3 ms. The contribution of TM to peak sodium current is ~90%, but 20 ms later it represents less than 1% of the total I_{Na}. This gating mode alone adequately reproduces the transient phase (0-5 ms) of I_{Na} but fails to explain the sustained component 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 (Figure 1). Increased transition rate from inactivated to open state and reduced probability toward absorbing second inactivated state results in long lasting (100-300 ms) activity before terminated by the absorbing state. These non-inactivating bursts has been already known from both skeletal and cardiac muscle and were referred as slow, non-inactivating, or "cloudburst" currents [29-31]. Facilitation of BM were reported from cardiac muscles after chemical intervention and termed 'failure of inactivation' [32]. Channels display BM 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 TM component of I_{Na} decays following the peak, the relative contribution of BM to total current can grow as high as 50%. BM current then declines and 200-300 ms later it is replaced by the third gating mode referred as *Late Scattered Mode* (LSM). LSM can be derived from TM 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 (Figure 1).

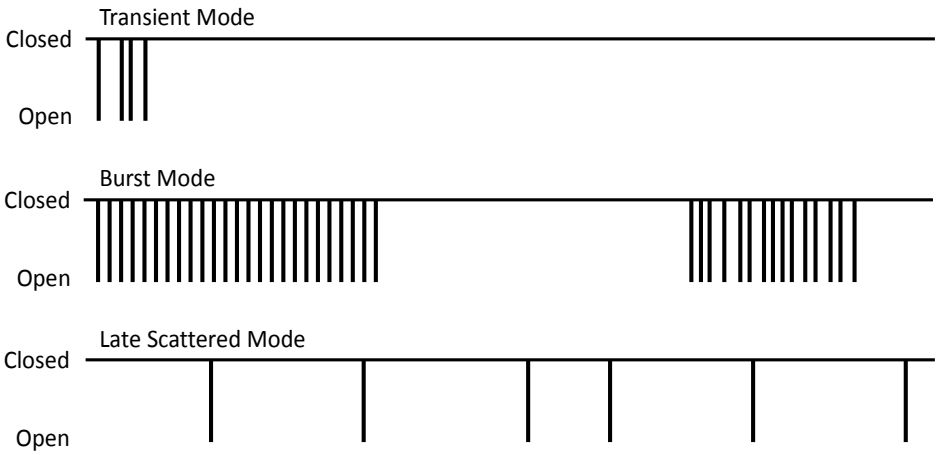

Figure 1. Schematic illustration for different channel activity patterns contributing to late sodium current.

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 TM; 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 BM and LSM. The contribution of BM and LSM to $I_{Na,L}$ is equal at the beginning of this phase, then monotonic reduction of BM leaves LSM the only gating mode shaping the plateau 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 [33-42]. Targeted pharmacological modulation of different gating modes is hoped to exert cardioprotective and antiarrhythmic effects [43-45] .

3.2. Window Currents

The “window” region is the voltage range where the steady state activation and inactivation curves of sodium channels overlap. In the window region channels may recover from inactivation then 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 identity of $I_{Na,L}$ is discussed in the literature, the flip-flopping of the Na channel in the 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 below -60 mV, far below the plateau voltage (about 0 mV) in most species reducing the probability for open state [2, 46]. Additionally, the current in the window region is very small in healthy conditions where the crossing point is less than 5% of the I/I_{max} [23, 46-48]. These two factors acting in synergism result in a small participation of window mechanisms to $I_{Na,L}$. Furthermore, experimental observations presented by *Beyder et al.* indicate that shear stress shifts the window significantly to negative direction [49]. 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, mutations or pathologic regulation of the channel might shift either steady state activation or inactivation curve altering the position and size of the window hence changing its contribution to $I_{Na,L}$ [14].

3.3. Non-equilibrium gating

Different gating modes and the concepts of window current describe well the behavior of sodium current elicited with square pulses. However, when sodium channels are positioned in functioning cardiac cells they are exposed to dynamically changing voltage. Experimental data show that $I_{Na,L}$ is facilitated when evoked with repolarizing voltage ramp or AP shape command [18-20]. Traditional Markovian models fail to reproduce this phenomenon, but *Clancy et al.* [18] proposed a new mechanism named 'non-equilibrium gating' that can explain these observations. 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 most fascinating 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. Earlier models used simplified conditions and did include this '*history factor*'. *Magyar et al.* provided strong experimental evidence to support the non-equilibrium gating hypothesis. They demonstrated that opening probability of the sodium channel is higher during voltage ramp than that of observed with constant (rectangular) voltage command and sodium current duration depends on the duration of ramp [19]. Further, indirect evidence supporting this hypothesis were provided by *Horvath et al.* when they showed that the magnitude of $I_{Na,L}$ is comparable with those of major potassium currents and the current profile is determined by the voltage profile of AP in ventricular myocytes [20]. These observation led them to the conclusion that non-equilibrium gating is the chief factor determining the profile of TTX sensitive current during AP [20]. Non-equilibrium gating theory does not preclude the involvement of other gating modes to $I_{Na,L}$. 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 [43, 50, 51] understanding the mechanism behind $I_{Na,L}$ can help to develop new antiarrhythmic drugs or strategies.

3.4. Non-cardiac sodium channels in the heart

Association of ECG abnormalities to epilepsy [52, 53] and myotonic disorders [54, 55] raised the possibility that the same mutated sodium channels which are responsible for hereditary diseases of nervous system or skeletal muscles might cause repolarization abnormalities in the heart. Later, several 'non cardiac' isoforms were identified in cardiac tissue by functional tests based on voltage dependency and drug sensitivity in different species [37, 56-58]. 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 heart of multiple species [58-63]. According to the report of *Westenbroek et al.*, non-cardiac isoforms represents a substantial fraction (23%) of the total number of sodium channels in mouse heart [60]. Moreover, the distribution of different isoforms show characteristic patterns. While the cardiac isoform $Na_v1.5$ is localized preferentially to the sarcolemma including intercalated disks 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. $Na_v1.4$ and $Na_v1.6$ showed low level surface staining. These data indicate that cardiac and non-cardiac isoforms of sodium channels have different role 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 is to couple the electric signal to calcium dynamics [59, 60]. This sharp functional distinction might be questioned by earlier work of Malhotra et al. who observed colocalization of $Na_v1.1$ and $Na_v1.5$ isoforms in rat myocardium [64].

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 $I_{Na,L}$? *Biet et al.* addressed this question and the data they presented suggests 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 [56]. This observation has been confirmed by Yang et al. reporting that $Na_v1.8$ provide the 38% of $I_{Na,L}$ [57]. 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 establish a new strategy in antiarrhythmic therapy.

4. The Physiology of plateau sodium current

Several membrane 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 dV/dt being close to zero [65]. Because 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 voltage near the plateau voltage. This synergistic interplay between currents and voltage during the plateau have significant impact on the time course of terminal repolarization, thus duration of the AP [66].

4.1. Contribution of plateau sodium current to cardiac electric activity

Most of our current knowledge on the electrophysiology of $I_{Na,L}$ originates from experiments employing rectangular voltage command and computer simulations based on these data. These results predicted a tiny flat current present during the whole length of AP. The extent of contribution of $I_{Na,L}$ to shaping AP under physiologic conditions was a subject of debate because of its small magnitude. Nevertheless two complementary lines of experimental evidence indicated that the plateau sodium current affected the AP. First, TTX block shortened the AP [8, 10] and second, facilitation of $I_{Na,L}$ lengthened the AP [20, 67]. Furthermore, an increasing number of observations indicate that the magnitude of $I_{Na,L}$ was markedly underestimated in earlier reports. When using ramp or AP shape command, there is a substantial increase in current magnitude [18, 19]. Recent publication employing self-action potential technique indicates that the magnitude of the current during plateau is comparable to those of delayed potassium currents [20].

We have only a small number of reports displaying direct recording if $I_{Na,L}$ during AP where the late component is not distinguishable from the early, transient phase. When cardiac sodium current is measured by rectangular command, it can be fitted by multiexponential function and the late component is a smooth continuation of the decaying early phase. When $I_{Na,L}$ is recorded under AP command, there are two major type of profiles observed. In the first case the current magnitude decays monotonically; this profile was observed in dog and predicted by some of the models [68-70]. In the second type, the decay of transient phase is followed by a slow current accumulation during the plateau, then it forms a peak before the terminal repolarization of AP and declines rapidly reaching zero when membrane potential returns to resting level. This saddle-like profile was reported from human [71], canine [72], and guinea pig heart [20, 73]. These differences might arise from interspecies variances of AP shape, but the impact of methodological differences cannot be excluded either.

I_{Na} is a key player in propagation of cardiac electric activation in the myocardium [63, 74] and in less extent to pacemaker activity especially in young age [75]. Due to the contribution of plateau sodium current to AP duration $I_{Na,L}$ has strong influence in determining QT distance of the ECG. Increased $I_{Na,L}$ is associated with lengthened QT interval (Long QT syndrome) and increased risk for arrhythmia [47, 76-81]. In accordance with this, inhibiting $I_{Na,L}$ was shown to shorten QT interval [82, 83]. Mutations resulting in facilitation of late sodium current are associated with increased QT dispersion too [52, 82]. How increased $I_{Na,L}$ leads to increased QT dispersion is not completely understood, but transmural heterogeneity of sodium current is probably also involved [72, 84]. QT dispersion is determined routinely in clinical cardiology and regarded one of the most valuable predictor for arrhythmias [85, 86]. Thus, increased repolarization inhomogeneity due to pathologic $I_{Na,L}$ might be 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, 87-92], slow impulse propagation [23, 93, 94], familiar atrial fibrillation [95, 96] and sick sinus syndrome [97, 98]. Cases, where sodium channel mutations were associated with cardiomyopathy were reported often with electric disturbances [99-101]. 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 densities of cardiac ionic currents and AP shape are present in ventricles [102-105]. Differences in sodium current magnitude between epicardial and endocardial cells were also observed in canine and murine heart [72, 84, 106]. According to these reports $I_{Na,L}$ is 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 [107-109]. This coincidence might indicate 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 [110]. 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). 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, conclusion that has been confirmed by others [111, 112]. The involvement of late sodium current in rate adaptation could explain why $I_{Na,L}$ facilitation caused by mutant sodium channel was found to increase the risk for arrhythmias following frequency changes [110].
The results of Lowe et al. [77] adds support to the connection between $I_{Na,L}$ and arrhythmias. Lowe et al. reported 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 intra-myocardial inhomogeneity of calcium and potassium currents in females [113-120].

4.3. $I_{Na,L}$ and calcium homeostasis of cardiac cells

Sodium channels are cardinal route for Na^+ into cardiac cells. In spite of the small magnitude of plateau sodium current, there is a consensus that the contribution of the sustained component provides a significant fraction (30-50%) of the total sodium entry [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 [121-123]. Apart from the impact on the sodium homeostasis of cardiac cells, $I_{Na,L}$ is implicated in modulation of the calcium homeostasis as well. Increased cytosolic Na^+ level is translated to elevated cytosolic calcium concentration and known to induce positive inotropic response [121, 124]. Calcium homeostasis in linked to $I_{Na,L}$ by multiple ways.

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. The longer depolarization prolongs the time while L-type calcium channels remains open and increases the amount of Ca^{2+} entering to the cytoplasm. The profile of L-type calcium current (LTCC) was subject of debate for long time. Model studies based on experimental data from traditional voltage clamp experiments employing rectangular voltage command predicted divergent dynamics during AP. Some of the models indicated that LTCC is present only under early plateau then it declines [125, 126]. 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 LTCC is present during the entire plateau and declines with the terminal repolarization in all mammalian models studied [105, 127-130]. Therefore, lengthening the AP adds significant amount of Ca^{2+} to influx via L-type calcium channels. The mechanism what prevent the inactivation of LTCC at these positive membrane potential is not completely understood, but reopening of inactivated channels has been demonstrated during maintained depolarization [130, 131]. Another possible mechanism for sustained LTCC could be the calcium window current. The crossing point for activation and inactivation curves is found between -20 and 0 mV allowing a subpopulation of L-type calcium channels to flip-flop between open and inactive state [71, 132, 133]. Another mechanism that could maintain LTCC during plateau is the non-equilibrium gating mechanism discussed earlier with relation to sustained sodium current [2, 18, 19]. 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 [134]. 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 [135]. However, subsequent 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 [136, 137]. Later, TTX sensitive calcium currents were reported from multiple animal models strengthening the evidences against the slip mode conductance hypothesis [69, 138-140]. 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 revived. It has been known for 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 decrease the Na^{+} selectivity resulting in a channel permeable for Ca^{2+} [141-144]. Knowing the increasing number of sodium channel mutations [5, 81, 95, 97, 101, 145-147] associated with diverse impact on the electrophysiology and deteriorating effects on ionic homeostasis of cardiac myocytes we can postulate that some mutation, still not known, might involve altered ion selectivity.

4.3.3. Interaction of $I_{Na,L}$ and sodium/calcium exchanger

The function of NCX in cardiac myocytes is highly complex [148-152]. NCX transports Ca^{2+} into or out of the cell depending on the cell's thermodynamic state that is the membrane voltage and the gradients of Na and Ca^{2+} across the membrane. Starting at the late systole and through the diastole, NCX removes Ca^{2+} from cytoplasm exchanging it with Na^{+} (forward mode) [129, 151]. This function is crucial for restoration of diastolic Ca^{2+} level and long term calcium homeostasis. However, when the membrane is depolarized and the transient Na current increases the subsarcolemmal Na^{+} concentration the net driving force for the Na^{+}/Ca^{2+} electrochemical gradient is reversed and NCX transports Ca^{2+} into the cytoplasm while removing Na^{+} (reverse mode) [129, 151]. Increasing Na^{+} concentration in the cytoplasm shifts the Na^{+}/Ca^{2+} equilibrium resulting in inhibition of removal and facilitation of calcium entry. The mechanism is analogue to the digitalis induced Ca^{2+} load leading to elevated cytosolic Ca^{2+} level [149, 153].

5. Modulation of late sodium current

The heart adapts to changing conditions, like physical activity, environmental stress or emotional state. This adaptation requires moment-to-moment fine tuning of all ion channels and transporters, including sodium channels. The sustained component of sodium current is modulated by several physiologic and pathologic factor.

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) and Ca^{2+} - CaM dependent protein kinase (CaMK). These components modulate $I_{Na,L}$ individually and cooperatively [154-156]. 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 [36, 154, 157]. 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) [158]. 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 diverse functional disturbances.

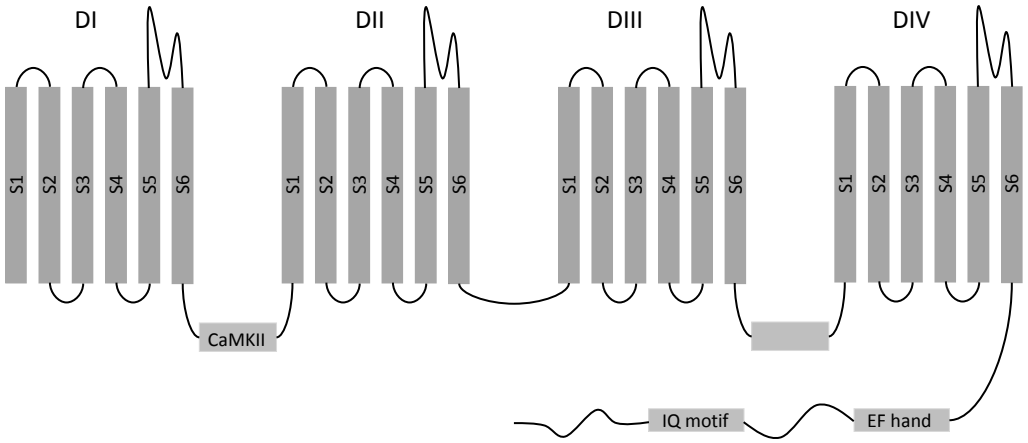

Figure 2.
Schematic representation of the structure of the α-subunit of cardiac sodium channel
Each domain (DI-DIV) consists of six transmembrane segments (S1-S6) interconnected by intracellular and extracellular loops. The intracellular loop between DI-DII is the target region for CaMKII, DIII-DIV loop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

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 or not. The question was addressed by Wingo et al. in 2004 and based on their observations they proposed that Ca^{2+} binds directly to a dedicated motif located close to c-terminus and modulates Na^{+} channel function [159]. This conclusion was supported by several 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 (Figure 2). Second, using NMR spectroscopy it was demonstrated that Ca^{2+} effectively binds to this EF hand. Third, voltage clamp experiments revealed that SSI is shifted toward positive voltages in high cytosolic Ca^{2+} even in the presence of a CaM inhibitor peptide. Furthermore, mutations in the EF hand prevented both Ca^{2+} binding to EF motif and high Ca^{2+} induced SSI shift. These undeniably consistent observations led the authors to the conclusion that Ca^{2+} exerts direct regulatory effect on sodium channel. However, confliction observations from several groups supported that CaM is essential to mediate Ca^{2+} effect and Ca^{2+} does not regulate sodium channel directly [160, 161]. The most important criticism against Wingo and co-workers' conclusion was that it is not known how effectively the inhibitory peptide they used prevents binding of CaM to sodium channels within the cell [158]. To resolve the conflicting results reported by so many independent experimenters a new model was proposed by Shah et al [162]. 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 the 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 his 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 [163]. They also proposed that CaM-mediated regulation is latent in cardiac sodium channel unless it is unmasked by mutations of the EF hand, or very low Ca^{2+} level in cytoplasm.

5.1.2. Calmodulin

Calmodulin (CaM) is a ubiquitous calcium sensing protein that mediates Ca^{2+} effects within wide variety of cells, including cardiac myocytes [160, 161]. CaM was shown to interact with the IQ motif of sodium channel and regulate gating mechanism [158, 160, 164]. The three dimensional configuration of CaM resembles to 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+}. 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 [165]. This linker region is considered the inactivation gate of sodium channel [166]. When Ca^{2+} concentration is low and CaM does not bind 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 [162, 165, 167]. When Ca^{2+} is elevated, Ca^{2+}/CaM complex (holo-CaM) is formed with different structure and affinity for the IQ motif is reduced by a magnitude [162]. 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 [165]. Nevertheless, the holo-CaM/DIII-IV interaction is not the only possible mechanism to induce the rightward shift of SSI by high Ca^{2+}, because IQ motif deleted sodium channels retain Ca^{2+} sensitivity [163]. As it was discussed above, Ca^{2+} can bind to the EF-hand of C-terminus altering the voltage sensitivity of inactivation too. Parallel to the direct regulation on sodium channel, CaM activates Calmodulin Kinase that also modulates the channel kinetics [168].

5.1.3. Calmodulin Kinase

Cardiac calmodulin kinase is a serine/threonine kinase implicated in a multitude of cellular function in vide variety of cells including cardiac myocytes. Cardiac cells express dominantly two isoforms of calmodulin kinase type II (CaMKII) referred as nuclear (δ_B) and cytoplasmic (δ_C) types; sodium channels are regulated by the cytoplasmic isoform [154, 169, 170]. It is now well established that CaMKII phosphorylates sodium channels at multiple sites resulting in complex effects and leading to increase of $I_{Na,L}$ [164, 171, 172]. Generally, upregulation of CaMKII was shown to induce a shift in SSI to depolarizing direction, enhance slow or intermediate inactivation and facilitate recovery from inactivation. Each of these effects individually and collectively enhance $I_{Na,L}$. While substantial interspecies differences were reported on the impact of CaMKII induced phosphorylation on sodium channel gating, the integrated effect is always stimulation of the late component of sodium current, and inhibition of the enzyme reduces $I_{Na,L}$. Wagner and his co-workers reported negative shift of SSI in rabbit cardiac myocytes following overexpression of CaMKII [171]. This observation was confirmed in expression system using HEK293 cells by Ashpole et al and Koval et al [172, 173]. In contrast, when Aiba and his co-workers used freshly isolated guinea pig ventricular myocytes and CaMKII was added to the pipette solution, they observed a positive shift in SSI [164]. Observations regarding the activation of current are discordant too. Young and Caldwell reported a hyperpolarizing shift in the voltage dependence of activation [174], whereas no effect was seen by others [164, 171, 172, 175]. Aiba et al also reported increased peak amplitude for the transient phase of sodium current [164], while others reported no change in this parameter [171-173]. 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 [164]. Nevertheless, all reports are consistent in that CaMKII enhances the fraction of channels undergoing intermediate or slow inactivation. Resultantly, CaMKII upregulation facilitates $I_{Na,L}$ that is reversible with CaMKII inhibitors. The link between increased CaMKII activity and facilitated $I_{Na,L}$ was confirmed in both healthy and diseased myocardium by others [157, 176, 177].

5.2. Cellular Metabolism

Metabolic activity of cardiac myocytes adapts to the momentary changes of the cardiac output, blood pressure or 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 [178], and cardiac sodium current is known to be modulated by these substantial increase in proton concentration [68, 179-182]. There is a consensus on that acidosis reduces the magnitude and the decay of the transient phase. Furthermore, positive shift in voltage dependency of activation and inactivation was observed in Xenopus expression system [180-182]. Additionally, Jones et al. demonstrated an increase in window current and deceleration of time constant of slow inactivation in Xenopus oocytes. Based on these data they predicted AP lengthening at low pH in a computer model [180]. Murphy et al. reported depolarizing shift in voltage dependency of activation, but not in SSI in freshly isolated canine ventricular myocytes [68, 179]. In agreement with Jones et al., they observed the prolongation of AP at low pH, but they found that $I_{Na,L}$ was reduced at in both endocardial and epicardial cells [68].

Acute and chronic hypoxia is known to induce electric disturbances in myocardium leading to arrhythmia. Several study addressed the effect of hypoxia on $I_{Na,L}$ and all observations, employing wide variety of experimental model consistently showed that hypoxia increases the late sodium current [11, 183-187]. Wang et al. studied the mechanism of hypoxia induced $I_{Na,L}$ facilitation [183]. 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 SSI curve resulting in significant reduction of transient I_{Na} 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 shaping AP in cardiac cells.

Hydrogen peroxide and free radicals were demonstrated to stimulate $I_{Na,L}$ by several team [122, 188-190]. In accordance with these observations, specific $I_{Na,L}$ inhibitor ranolazine or TTX attenuated the AP lengthening effect of H_2O_2 [190]. However, Erickson and his co-workers showed that free radicals can directly activate CaMKII [191]; 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} [192]. The reduction develops from hyperpolarizing shift in SSI and activation curve decreasing the window current. An ischemic metabolite, lysophosphatidylcholine was also demonstrated to reduce transient I_{Na}, but effects on $I_{Na,L}$ has not been addressed in these studies [12, 193]. Nitrogen oxide was found to facilitate $I_{Na,L}$ by Ahern and co-workers fifteen years ago; they proposed that nitrosylation of sodium channels within its own plasma membrane modify the gating of cardiac sodium channel [194]. Since then the mechanism has been confirmed by Cheng et al. demonstrating that caveolin-3 as mediates sodium channel nitrosylation [195].

5.3. Mechanical stress

Myocardial wall tension is subject of moment to moment change during cardiac cycle and ion channels embedded into the cell membrane experience variable mechanical stress. It is now well established that cardiac sodium channels respond to mechanical stress with altered gating function [49, 196]. 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} [49]. Increased stretch of the patch resulted in a negative shift in both SSI and activation curve and decelerated recovery from inactivation. Interestingly, the membrane stress increased the number of available channels under the patch, leading to increase in peak current. Recently, the same group confirmed these observations on freshly isolated mouse ventricular cells [197]. Moreover, in the same publication authors demonstrated that ranolazine inhibits the mechanosensitivity of cardiac sodium channels on 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 and published from the same team subsequently [198]. Ranolazine is antiarrhythmic drug known to target cardiac sodium channels and inhibiting $I_{Na,L}$ with high selectivity over $I_{Na,T}$ [43, 51, 123, 199, 200]. Considering that myocardial wall stretch is known to play key role in arrhythmogenesis [201-203] these data may establish a new therapeutic strategy in antiarrhythmic pharmacology. Currently, pharmacological reduction of preload with diuretics and vasodilators is the only possibility to reduce wall stress and prevent disease progression in

arrhythmogenic right ventricular cardiomyopathy [204, 205]. Reducing mechanical sensitivity of the electric system in cardiac myocytes might open a new direction.

6. The plateau 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, 41, 44, 57, 77, 100]. 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]. 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) sodium channels are the major route for sodium into the cell. 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 [206, 207].

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 [150]. 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 [121, 122]. 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 [70, 149, 150, 208, 209]. Ca^{2+} is the key regulator of the majority of functions in cardiac myocytes, including metabolism, electric activity, contractility as well as apoptosis [154, 169, 170, 209-212]. Elevated cytosolic calcium leads to Ca^{2+} overload in sarcoplasmic reticulum resulting in contractile dysfunction and increased risk for arrhythmia [51, 213-217].

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, 41, 57, 123, 214, 215]. 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 [218, 219]. 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, 96, 133]. Calcium overload was documented also to promote the generation of EAD but the mechanism is not completely understood [220, 221]. However, it has been proposed that spontaneous calcium release from sarcoplasmic reticulum might facilitate I_{NCX} and induce membrane oscillations [133, 218, 220, 221]. Horvath and his co-workers recently investigated the role of $I_{Na,L}$ in

generation of EAD [20]. 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) [38, 222]. 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 [223-226]. 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, 84, 189, 227, 228]. Increased beat to beat variability results from reduced repolarization reserve and makes the heart more vulnerable to potentially proarrhythmic prolongation of the APD [229]. Regional differences in AP duration are generally attributed to asymmetrical distribution of various ion channels [105, 230-235]. 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 [236, 237].

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 [99, 238]. 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 [239]. 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 [101, 240]. 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 [241]. They proposed that acidification of cardiac myocytes may cause the DCM phenotype of these patients.

7. The plateau 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 [20, 121, 123]. Other activators like ouabaine or Pyrethroids are also used for research purposes but held more 'dirty' [6, 121].
Pharmacological suppression of plateau sodium current was shown beneficial to reduce contractile dysfunction and arrhythmic activity in several pathologic model [45, 197, 214, 242-245]. 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 (Figure 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 [246-248]. Mixed ion channel blocker amiodarone has outstanding $I_{Na,L}/I_{Na,T}$ selectivity amongst traditional antiarrhythmic drugs [249], but chronic amiodarone is documented to carry severe side effects preventing its use in long term therapy [250-259].

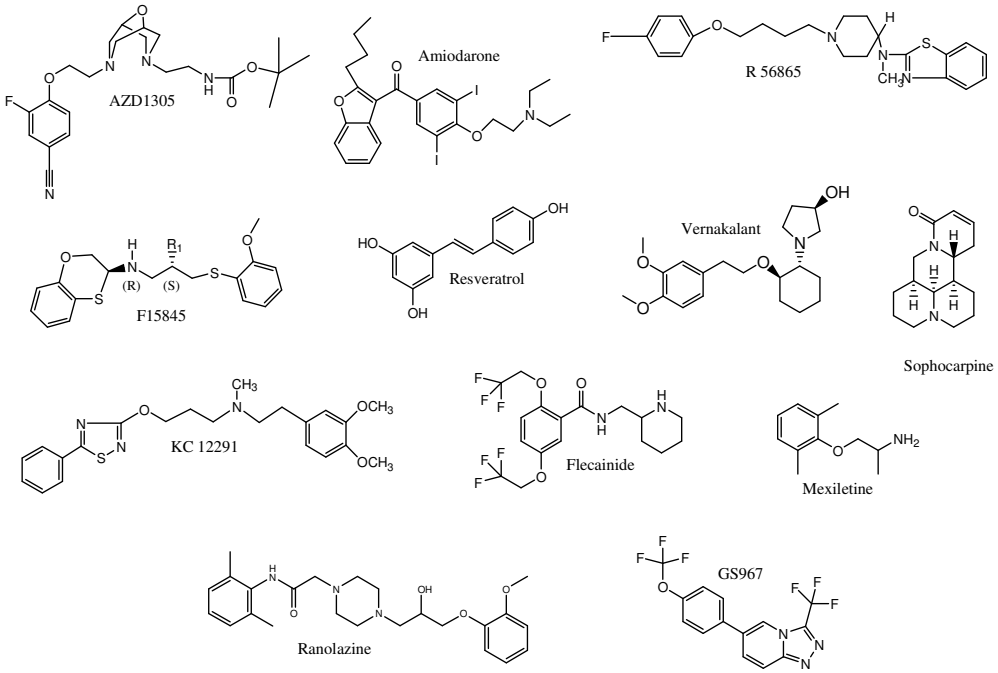

Figure 3.
Chemical structures of $I_{Na,L}$ inhibitors.

The first, highly selective $I_{Na,L}$ blocker with no known adverse effects was Ranolazine, an anti-ischemic, antianginal drug [244, 245]. Ranolazine (Figure 3) effectively inhibits late sodium current with 17 and 1300 μM EC_{50} for $I_{Na,L}$ and $I_{Na,T}$ respectively [123]. 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 [197, 198, 214]. However, Ranolazine reduces I_{Kr}, I_{NCX} and $I_{Ca,L}$ with EC_{50} value between 12-90 μM and blocks catecholamine receptors too [260, 261]. 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 (Figure 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} [123].
An interesting work was published in 2013 by an international team in PACE [262]. 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.

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

Name	EC_{50}	Effective cc.	Selectivity
AZD1305	4.3 μM [263]		EC_{50} for $I_{Na,T}$: 66 μM [263]
F15845	5.3 μM [264]		
GS967	0.13 μM [123]		$I_{Na,T}$: 7.5% inhibition at 10 μM [123]
KC 12291	9.6 μM [265]		25% I_{K1} inhibition at 10 μM; 42% I_{to} inhibition at 10 μM [266]
R 56865	200 nM [267]		Binds to α_1-adrenoceptors, 5-HT receptors, DHP receptors with K_i between 20-340 nM [268]
RSD1235 (Vernakalant)	31 μM [269]	30 nM [270]	EC_{50} for Kv1.5, Kv4.2 and Kv4.3: between 10-40 μM; I_{K1}: 1 mM; $I_{Ca,L}$: 220 μM [269]
Amiodarone	6.7 μM [249]		EC_{50} for $I_{Na,T}$: 87 μM [249]; I_{Kr}: 2.8 μM [271]. Inhibits I_{K1} and I_{Ks} in concentration higher than 10 μM [272, 273]
Flecainide	3.4 μM [123]		EC_{50} for $I_{Na,T}$: 84 μM [123]
Mexiletine	18 μM [274]		EC_{50} for $I_{Na,T}$: 35 μM; No effect on $I_{Ca,L}$ up to 100 μM [274]
Ranolazine	17 μM [123] 6 μM [199]		EC_{50} for $I_{Na,T}$: 1329 μM [123]; EC_{50} for I_{Kr} : 12 μM, I_{NCX} : 91 μM, $I_{Ca,L}$: 50 μM [199]
Resveratrol	34 μM [275]		
Sophocarpine		30 μM [276] 20-80 μM [215]	Inhibits I_{NCX} in concentrations higher than 20 μM [215]
Wenxin Keli	4 μM [262]		EC_{50} for $I_{Na,T}$: 11 μM [262]

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