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The Role of Late I_{Na} in Development of Cardiac Arrhythmias

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Abstract

Late I_{Na} is an integral part of the sodium current, which persists long after the fast-inactivating component. The magnitude of the late I_{Na} is relatively small in all species and in all types of cardiomyocytes as compared with the amplitude of the fast sodium current, but it contributes significantly to the shape and duration of the action potential. This late component had been shown to increase in several acquired or congenital conditions, including hypoxia, oxidative stress, and heart failure, or due to mutations in *SCN5A*, which encodes the α-subunit of the sodium channel, as well as in channel-interacting proteins, including multiple β subunits and anchoring proteins. Patients with enhanced late I_{Na} exhibit the type-3 long QT syndrome (LQT3) characterized by high propensity for the life-threatening ventricular arrhythmias, such as Torsade de Pointes (TdP), as well as for atrial fibrillation. There are several distinct mechanisms of arrhythmogenesis due to abnormal late I_{Na}, including abnormal automaticity, early and delayed afterdepolarization-induced triggered activity, and dramatic increase of ventricular dispersion of repolarization. Many local anesthetic and antiarrhythmic agents have a higher potency to block late I_{Na} as compared with fast I_{Na}. Several novel compounds, including ranolazine, GS-458967, and F15845, appear to be the most selective inhibitors of cardiac late I_{Na} reported to date. Selective inhibition of late I_{Na} is expected to be an effective strategy for correcting these acquired and congenital channelopathies.

Keywords

Ion channel currents; Electrophysiology; Long QT syndrome; Sudden cardiac death; Cardiac arrhythmias

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Recent years have witnessed a resurgence of interest in the late component of the sodium current (late I_{Na}), particularly its role in development of cardiac arrhythmias and as a pharmacologic target for the prevention of life-threatening arrhythmias and sudden cardiac death. In this review, our principal aim is to discuss the molecular basis for late I_{Na}, its cellular distinctions, and its contribution to the electrophysio-logical function of the heart in health and disease. We refer the readers to recent reviews dealing with the characteristics of the cardiac late I_{Na} (Belardinelli et al. 2006; Noble and Noble 2006; Saint 2006, 2008; Zaza et al. 2008; Undrovinas and Maltsev 2008a; Maier 2009; Antzelevitch et al. 2011; Shryock et al. 2013) as well as reviews dealing with cardiac sodium channelopathies associated with a gain of function of late I_{Na} and its role in arrhythmogenesis (Zimmer and Surber 2008; Ruan et al. 2009; Amin et al. 2010; Rook et al. 2012).

1 Late I_{Na} and Its Relationship to Peak I_{Na}

Voltage-gated sodium channels mediate excitability of heart, nerve, endocrine, and skeletal muscle tissues. When membrane depolarization achieves threshold potential, the Na^+ channels open, thus giving rise to the “peak” I_{Na} and the rapid upstroke (phase 0) of the action potential (AP).

The sodium channel activates during phase 0 of the AP and largely inactivates within 1 ms at body temperature. Between 0.1 % and 1 % the current inactivates more slowly during the plateau of the action potential (AP) (Patlak and Ortiz 1985) with the time constant being between 75 and 450 ms in humans (Undrovinas et al. 2002; Maltsev and Undrovinas 2006). Amplitude of the late component being small compared with the peak I_{Na} is large as compared with other ionic currents during AP plateau, e.g., around 0.5 pA/pF in normal human and canine ventricular myocytes (Maltsev and Undrovinas 2006; Undrovinas et al. 2006). Late I_{Na} amplitude varies depending on cell type, species, and conditions of measurement (e.g., holding and test potentials, temperature, duration of test pulse, and intracellular Na^+ concentration). Late I_{Na} amplitude is reported to be around 0.1 % of peak I_{Na} in rat (Patlak and Ortiz 1985) and guinea pig (Kiyosue and Arita 1989), but can reach 1 % in human (Maltsev and Undrovinas 2006) ventricular myocytes. It had been shown that all components of I_{Na} inactivation are due to different modes of gating of the same cardiac variant ($Na_V1.5$) of the sodium channel (Maltsev et al. 2009).

The amplitude of late I_{Na} is largest in M cells (Eddlestone et al. 1996) and in Purkinje fibers and much smaller in epicardial or endocardial cells in the canine heart. The more prominent late I_{Na} contributes to the longer AP and greater rate dependence of AP duration in M cells and Purkinje fibers (Eddlestone et al. 1996; Zygmunt et al. 2001) and thus to transmural dispersion of repolarization. Tetrodotoxin (TTX) is reported to inhibit late I_{Na} and abbreviate APD more in M cells and Purkinje fibers than in epicardial cells in the dog heart (Zygmunt et al. 2001; Coraboeuf et al. 1979), thus reducing the transmural dispersion of repolarization. In the guinea pig heart, however, late I_{Na} has been reported to be smaller in mid-myocardial than in epicardial and endocardial cells (Sakmann et al. 2000). The difference appears to be due to methodological considerations. Experiments involving isolated tissues indicate that the guinea pig heart is similar to that of the dog, containing M and transitional cells in the midmyocardium and cells with much briefer APD, showing little

response to I_{Kr} block, in the endocardial and epicardial layers (Sicouri et al. 1996). However, unlike the dog, dissociation of myocytes from smaller hearts is fraught with problems because epicardial and endocardial cells are under-represented (Antzelevitch et al. 1999). Indeed, studies involving dissociation of myocytes from guinea pig hearts have reported cells with electrophysiological and pharmacological profiles of M and transitional cells, but not of endocardial or epicardial cells (Bryant et al. 1998). Rather than lacking M cells, the studies reported by Sakmann et al. (2000) may be lacking in epicardial and endocardial cells.

At the single channel level, late I_{Na} is predominantly due to sodium channel reopenings during the plateau of the AP (Maltsev and Undrovinas 2006), which allow a relatively small but persistent influx of Na^+ into the cell. Such activity may be the result of single or bursts of openings of Na^+ channels (Fig. 1) (Patlak and Ortiz 1985; Undrovinas et al. 2002; Kiyosue and Arita 1989; Liu et al. 1992; Saint et al. 1992; Maltsev et al. 1998). The magnitude of the late I_{Na} is increased when the channel fails to enter the inactivated state after the initial opening. Sodium channel toxins including aconitine, veratridine, and sea anemone toxin II (ATX-II) prevent the sodium channel transition into the inactivated state, thus increasing late reopening of the channel, measured in excised or cell-attached patches during long voltage-clamp pulses (>200 ms).

2 Causes of an Enhanced Late I_{Na}

The magnitude of late I_{Na} in cardiac myocytes increases in several acquired or congenital conditions such as heart failure (Maltsev et al. 2007; Valdivia et al. 2005), hypoxia (Hammarstrom and Gage 2002), inflammation (Ward et al. 2006), and hyperthyroxinemia (Harris et al. 1991), or due to mutations in *SCN5A*, which encodes the α-subunit of the sodium channel (Rivolta et al. 2001), as well as in channel-interacting proteins, including multiple β subunits and anchoring proteins. Such an increase of late I_{Na} can be reproduced experimentally by application of natural and synthetic toxins [see (Honerjager 1982) for review] such as ATX-II, veratridine, and aconitine that bind to various sites on the Na^+ channel (Denac et al. 2000). It is important to make the distinction between toxins that bind near the local anesthetic binding sites (veratridine and aconitine) and those that bind to the sodium channel at unrelated sites (e.g., ATX-II). It had been shown that these compounds can cause arrhythmias when applied to intact or isolated heart preparations. For example, local application of aconitine causes atrial ectopic activity (Scherf et al. 1948) and ventricular tachycardia and fibrillation (Lu and De 1993). Bursting behavior, which results in a larger late I_{Na}, is reported to be increased as a consequence of some LQT3 mutations including ΔKPQ (Hartmann et al. 1994) and Y1795C (Rivolta et al. 2001). Table 1 lists the conditions and agents that are known to increase cardiac late I_{Na}.

3 Acquired Causes of an Enhanced Late I_{Na}

Ischemia is the most common pathology associated with enhanced late I_{Na}. An increase in late I_{Na} during ischemia contributes to the intracellular Na^+ loading observed in the ischemic heart (Xiao and Allen 1999; Liu et al. 2007; Tang et al. 2012). Simulated-demand ischemia was found to increase oxidative stress, late I_{Na}, and cytosolic Ca^{2+} levels in rabbit isolated

myocytes; the rise of intracellular Ca^{2+} was reduced by inhibitors of late I_{Na} and Na^+/Ca^{2+} exchanger (NCX) and by the free radical scavenger Tiron (Zhang et al. 2008). Activity of NCX is markedly increased by reactive oxygen species during re-oxygenation (Eigel et al. 2004). Hydrogen peroxide, nitric oxide, and thrombin are all reported to increase cardiac late I_{Na} (Ward and Giles 1997; Song et al. 2006; Ahern et al. 2000; Pinet et al. 2008). Nitric oxide (Ahern et al. 2000), hydrogen peroxide (Song et al. 2006), hypoxia (Ju et al. 1996), glycolytic metabolites (Kohlhardt et al. 1989), lysophosphatidylcholine (Undrovinas et al. 1992), and heart failure (Maltsev and Undrovinas 2006) also increase the incidence of bursts of Na^+ channel late openings that contribute to late I_{Na}. Protein kinases including CaMKII, PKC, AMPK, and PKA are activated during ischemia. Calcium and reactive oxygen species activate CaMKII and PKC (Erickson et al. 2011; Barnett et al. 2007), lysophosphatidylcholine activates PKC and tyrosine kinase (Murray et al. 1997), loss of ATP and elevation of AMP stimulate AMP-activated protein kinase, and norepinephrine release from cardiac nerve terminals leads to activation of PKA and increased L-type Ca^{2+} current. Each of these kinases, as well as intracellular Ca^{2+}, can modulate Na^+ channel function or expression.

Late I_{Na} is increased in myocytes isolated from failing human and dog hearts (Undrovinas and Maltsev 2008a; Undrovinas et al. 2002; Maltsev et al. 1998, 2007; Valdivia et al. 2005; Undrovinas et al. 1999), although peak I_{Na} is decreased (Undrovinas et al. 2002; Zicha et al. 2004). I_{Na} inactivates more slowly in cells isolated from failing hearts and the magnitude of late I_{Na} is 2–5 fold greater (Maltsev et al. 2007; Valdivia et al. 2005). Most $Na_V1.5$ channels in ventricular myocytes are localized near the intercalated discs where they interact with βIV-spectrin (Hund et al. 2010) and the rest are in the T-tubules and other areas of the plasma membrane. It is not known whether Na^+ channels located in these different regions of the cell are differentially regulated in terms of their late current in normal and/or diseased hearts.

The final common pathways leading to an increase of late I_{Na} in the failing heart, as in ischemia, may be ROS-induced oxidation and Ca^{2+}-induced kinase activation and phosphorylation of the Na^+ channel and/or channel-interacting proteins (Maltsev et al. 2008; Xie et al. 2009; Gautier et al. 2008). In the hypertrophied and/or failing heart, reduction of repolarizing current contributes to prolongation of AP duration in a nonuniform manner (Keung and Aronson 1981) and to alternans of Ca^{2+} transients and AP duration (Wilson et al. 2009), thus promoting an arrhythmogenic substrate.

4 Congenital Causes of Late I_{Na}

The long QT syndrome type-3 (LQT3) is caused by inherited “gain of function” mutations in the *SCN5A* gene [for reviews, see (Zimmer and Surber 2008; Ruan et al. 2009; Moreno and Clancy 2012; Blaufox et al. 2012)] and by mutations in Na^+ channel-interacting proteins that lead to an increase of late I_{Na} (Abriel 2010). The first description of an inherited LQT3 mutation, a deletion of amino acids 1,505–1,507 (ΔKPQ) in a patient with a prolonged QT interval, was presented in 1995 (Wang et al. 1995). The mutated *SCN5A* channel was heterologously expressed in HEK293 cells and demonstrated to cause an increase of late I_{Na} and of the duration of the action potential (Bennett et al. 1995; Wang et al. 1996). More than

80 different *SCN5A* mutations that increase cardiac ($Na_V1.5$) late I_{Na} have since been described in patients with LQT3. Most LQT3 mutations are missense mutations that cause late current by increasing the probability that the Na^+ channel will either fail to inactivate quickly or will reopen more readily from the closed state. Some of these mutations occur at sites that are also known targets for phosphorylation by protein kinases (Ahern et al. 2005). Sodium channel mutations such as ΔKPQ and Y1795C cause increased bursting activity of the Na^+ channel (Chandra et al. 1998; Clancy and Rudy 1999; Clancy et al. 2002) as do mutations in the IFM motif of the inactivation gate (West et al. 1992).

Four β subunits have been shown to play a critical role in cell surface expression, subcellular localization, as well as biophysical function of the Na^+ channels (Abriel 2010; Maier et al. 2004; Meadows and Isom 2005). Mutations in the Na^+ channel β subunits $Na_{v\beta}$ (β_1–β_4) are reported to be a cause of congenital LQT syndrome, atrial fibrillation, Brugada syndrome, and conduction slowing [reviewed by Abriel (2010)]. Loss of β_1 expression in mice results in increases of both peak and late I_{Na} and a prolonged QT interval (Lopez-Santiago et al. 2007). Late I_{Na} is increased in cells expressing *SCN5A* with the β_1, but not with the β_2, subunit compared to cells expressing *SCN5A* alone (Maltsev et al. 2009). Mutations in both β_3 and β_4 subunits have been identified in LQT3 and/or sudden infant death syndrome (SIDS) patients and found to cause an increased late I_{Na} when expressed with *SCN5A* in HEK293 cells (Medeiros-Domingo et al. 2007; Tan et al. 2010).

Numerous proteins are known to interact with the cardiac sodium channel (Rook et al. 2012; Abriel 2010; Vatta et al. 2006; Shao et al. 2009). Mutations in scaffolding and/or cytoskeletal “channel interaction proteins” (ChIPs) are recognized causes of LQT syndrome (Ackerman and Mohler 2010). Mutations in caveolin-3 (Vatta et al. 2006), alpha-1 syntrophin (Ueda et al. 2008; Wu et al. 2008a), and β_{IV} spectrin (Hund et al. 2010; Wu et al. 2008a; Sarhan et al. 2009; Vatta and Faulkner 2006) are associated with increased magnitude of late I_{Na} and with LQT and/or SIDS. Proteins such as F-actin, telethonin, α-actinin-2, and Z-band alternatively spliced PDZ-motif (ZASP) that are anchored at the Z-line may participate in the trafficking of ion channels to the T-tubule membrane (Vatta and Faulkner 2006). A mutation in telethonin is reported to increase Na^+ window current (Mazzone et al. 2008), and a missense mutation in ZASP shifts the voltage dependence of Na^+ channel activation (Li et al. 2010). Reduced interaction of the Na^+ channel with ChIPs such as the intercalated disc-associated proteins ankyrin-G and SAP97 may lead to a Na^+ channel loss-of-function phenotype such as conduction slowing or Brugada syndrome (Mohler et al. 2004; Scherer et al. 2008). Silencing of expression of SAP97 reduced peak I_{Na} in rat cardiomyocytes (Petitprez et al. 2011). The last three residues of the $Na_V1.5$ C-terminus associate with dystrophin protein complexes in the lateral membranes of cardiomyocytes, and a deficiency of dystrophin leads to decreased $Na_V1.5$ expression and myocardial Na^+ current (Petitprez et al. 2011; Gavillet et al. 2006).

5 Late I_{Na}-Mediated Arrhythmias

Patients with LQT3 syndrome are at a high risk not only for Torsade de Pointes (TdP) ventricular arrhythmias but also for atrial fibrillation (Benito et al. 2008; Darbar et al. 2008; Zellerhoff et al. 2009). In studies of isolated hearts and myocytes, enhancement of late I_{Na}

using ATX-II, veratridine, or aconitine is reported to cause arrhythmic activity in both atrial and ventricular tissues. In both inherited and acquired sodium channelopathies, late I_{Na} may be increased while peak I_{Na} is decreased (Maltsev et al. 2007; Valdivia et al. 2005; Zicha et al. 2004; Makita et al. 2008; Remme et al. 2006) and both can contribute to arrhythmogenesis.

Reduction in repolarization reserve can amplify the effect of an increase in late I_{Na} to delay repolarization, thus enabling the development of arrhythmias (Wu et al. 2004, 2006, 2008b, 2011)

6 Mechanisms Underlying Late I_{Na}-Induced Arrhythmogenesis

6.1 Late I_{Na} and Diastolic Depolarization: Abnormal Automaticity

Spontaneous diastolic depolarization responsible for pacemaking in sinoatrial and compact atrioventricular node cells is driven by ion currents including L- and T-type Ca^{2+} channel currents, “funny” current (HCN channels), and NCX [for reviews see (Chandler et al. 2009; Hoeker et al. 2009)]. Diastolic depolarization of myocytes in atrial and ventricular tissues is rare in the normal intact heart but is often observed in atrial cells and tissues excised from diseased human (Gelband et al. 1972; Escande et al. 1986; Mary-Rabine et al. 1980; Trautwein et al. 1962) and animal (Chen et al. 2000; Cheung 1981; Hogan and Davis 1968; Wit and Cranefield 1977) hearts.

A critical role for late I_{Na} in pacemaking was highlighted by recent studies demonstrating that atrial automaticity can be modulated by late I_{Na} enhancers and inhibitors (Song et al. 2009). Late I_{Na} was found to be present in atrial myocytes that undergo diastolic depolarization (Song et al. 2009). Sea anemone toxin II (ATX-II), a specific enhancer of late I_{Na} (Isenberg and Ravens 1984), accelerates diastolic depolarization and induces rapid firing of APs by atrial myocytes (Song et al. 2009). Reactive oxygen species H_2O_2 increases late I_{Na} and causes diastolic depolarization and rapid AP firing of atrial myocytes, which can be suppressed by block of late I_{Na} using ranolazine (1–5 μmol/L) or TTX (1 μmol/L) (Song et al. 2009). A slowly inactivating TTX-sensitive current, similar to late I_{Na}, was reported to contribute to diastolic depolarization of cardiac Purkinje cells (Carmeliet 1987a; Rota and Vassalle 2003) and of sinoatrial node cells (Baruscotti et al. 2000). In non-pacemaking ventricular myocytes, late I_{Na} was shown to be present at voltages as negative as −70 mV (Sakmann et al. 2000; Saint et al. 1992), well within the voltage range at which spontaneous diastolic depolarization can be observed in these cells (Escande et al. 1986; Mary-Rabine et al. 1980; Trautwein et al. 1962). Sicouri et al. (2012a) recently demonstrated an effect of ranolazine to suppress phase 4 depolarization in superior vena cava sleeves isolated from the canine right atria. These findings suggest that enhancement of late I_{Na} may be a potential cause of atrial arrhythmogenesis.

6.2 Late I_{Na}-Induced Triggered Activity

Early and delayed afterdepolarization (EAD and DAD) are important mechanisms of arrhythmic activity whose occurrence is facilitated when late I_{Na} is enhanced.

Late I_{Na} contributes to AP prolongation (Kiyosue and Arita 1989; Liu et al. 1992; Colatsky 1982). Because the magnitude of late I_{Na} is greater at slow heart rates (Wu et al. 2011; Jia et al. 2011) and the effect of late I_{Na} to increase AP duration is greater in mid-myocardial than in epi- or endocardial myocytes (Zygmunt et al. 2001; Sicouri et al. 1997a; Antzelevitch and Belardinelli 2006), the role of late I_{Na} to increase dispersion of repolarization and EAD formation is facilitated by heart rate slowing. A role for late I_{Na} in EAD formation is supported by findings that enhancers of late I_{Na} such as ATX-II and anthopleurin-A cause EADs and TdP (Isenberg and Ravens 1984; Ben et al. 2008; Boutjdir and El-Sherif 1991; Song et al. 2004; Ueda et al. 2004; Spencer and Sham 2005; Auerbach et al. 2011). Moreover, inhibitors of late I_{Na} reduce occurrences of EADs and TdP induced by I_{Kr} blockers (Abrahamsson et al. 1996; Shimizu and Antzelevitch 1997a; Orth et al. 2006; Wu et al. 2009a), heart failure (Maltsev et al. 2007; Undrovinas et al. 1999), or left ventricular hypertrophy (Guo et al. 2010).

While a modest increase in late I_{Na} may not cause significant prolongation of AP duration in the normal heart, it can facilitate APD prolongation and EADs induction by I_{Kr} and I_{Ks} blockers. Consistent with this observation, individual susceptibility to drug-induced long QT syndromes has been shown to be linked to *SCN5A* mutations (e.g., L1825P or Y1102) that augment late I_{Na} (Makita et al. 2002; Splawski et al. 2002). Patients with these Na^+ channel gene mutations have normal QT intervals prior to exposure to the drugs, but develop long QT intervals and TdP when given agents such as cisapride or amiodarone (Makita et al. 2002; Splawski et al. 2002). Experimental studies involving isolated hearts, tissues, or myocytes have shown that a small increase of late I_{Na} may facilitate the proarrhythmic effects of I_{Kr} and I_{Ks} blockers (Wu et al. 2006; Song et al. 2004), drugs such as cisapride, amiodarone (Wu et al. 2008c), and quinidine (Wu et al. 2008b), as well as "low-risk" drugs such as moxifloxacin and ziprasidone (Wu et al. 2006). As expected, inhibition of late I_{Na} by ranolazine attenuates the increase of AP duration and EAD induction caused by the combination of ATX-II and I_{Kr}-blocking drugs (Song et al. 2004, 2008). These observations suggest that enhanced late I_{Na} is a major risk factor predisposing cardiac myocytes to development of EADs under both acquired and inherited long QT conditions.

Delayed afterdepolarizations (DADs) have been recognized as a mechanism of digitalis-induced arrhythmogenesis distinct from diastolic phase 4 depolarization, for over 40 years (Ferrier et al. 1973; Wit and Rosen 1983). DADs are observed under conditions in which myocytes are overloaded with Ca^{2+}, causing spontaneous Ca^{2+} release from sarcoplasmic reticulum and Ca^{2+} waves during diastole, leading to aftercontractions (Kass et al. 1978; Kort et al. 1985; Marban et al. 1986; Capogrossi et al. 1987; Stern et al. 1988; Schlotthauer and Bers 2000; Tweedie et al. 2000; Fujiwara et al. 2008). The transient inward current I_{TI} generated by electrogenic Na^+/Ca^{2+} exchange is responsible for these DADs (Kass et al. 1978; Schlotthauer and Bers 2000; Fedida et al. 1987).

Enhancement of late I_{Na}, similarly to inhibition of the sodium–potassium pump by cardiac glycosides, causes Na^+ loading of myocytes. Late I_{Na}-mediated Na^+ loading reduces the driving force for Ca^{2+} efflux from the cell via NCX (Noble and Noble 2006; Shattock and Bers 1989), thereby increasing the diastolic Ca^{2+} concentration and Ca^{2+} uptake by sarcoplasmic reticulum, and reducing the rate and extent of diastolic relaxation (Fig. 2)

(Undrovinas et al. 2010; Sossalla et al. 2008). In the normal heart, Na^+ influx during the AP plateau is estimated to account for 30 % of total Na^+ influx at a heart rate of 60/min (Makielski and Farley 2006). Na^+ influx can be increased several-fold when late I_{Na} is enhanced by ischemia, lysophosphatidylcholine, H_2O_2, or *SCN5A* mutations (Makielski and Farley 2006) thus increasing the incidence of DADs (Song et al. 2008; Wu and Corr 1995). Similarly, in myocytes from failing hearts the late I_{Na} is increased by 50 % or more (Valdivia et al. 2005; Undrovinas et al. 2010; Undrovinas and Maltsev 2008b).

DADs induced by cardiac glycosides or other interventions are suppressed by inhibitors of late I_{Na}, including TTX, lidocaine, mexiletine, propafenone, R56865, and ranolazine (Song et al. 2008; Rosen and Danilo 1980; Zeiler et al. 1984; Vollmer et al. 1987; Sawanobori et al. 1987; Inomata and Ishihara 1988; Tsuchida and Otomo 1990; Damiano et al. 1991). Reduction of late I_{Na} by ranolazine and GS-458967, a selective and potent inhibitor of late I_{Na}, has also been shown to reduce the incidence of DADs in experimental studies of pulmonary vein and superior vena cava sleeves (Sicouri et al. 2012a, b, 2013) Blocking late I_{Na} using R 56865, ranolazine, or TTX has been shown to reduce Na^+-dependent Ca^{2+} loading of cardiac myocytes from normal and failing hearts (Song et al. 2006; Undrovinas et al. 2010; Sossalla et al. 2008; Haigney et al. 1994; Fraser et al. 2006). These findings implicate increased Na^+ entry into myocytes via Na^+ channels as a cause of Na^+ and Ca^{2+} loading of myocytes, and arrhythmogenic DADs, while inhibition of late I_{Na} can be used as a means of reducing occurrences of DADs.

6.3 Role of CaMKII Activation in Augmentation of Late I_{Na}

Positive feedback loops have been identified between increases in late I_{Na} and increased expression and activation of CaMKII. These feedback loops appear to contribute to the pathology of Na^+/Ca^{2+} overload in the failing and/or ischemic heart, where late I_{Na} (Saint 2006; Maltsev et al. 2007; Valdivia et al. 2005; Ju et al. 1996; Undrovinas et al. 1999; Le Grand et al. 1995) and expression and activity of CaMKII (Kirchhefer et al. 1999; Hoch et al. 1999) are increased. CaMKII phosphorylates phospholamban to increase Ca^{2+} uptake by sarcoplasmic reticulum (Ji et al. 2003) and RyR2 (Rodriguez et al. 2003) to increase the sensitivity of calcium release channels to Ca^{2+}-induced opening. These two events can lead to increased leak of Ca^{2+} from the sarcoplasmic reticulum during diastole (Maier et al. 2003; Ai et al. 2005; Guo et al. 2006; Sag et al. 2009; Sossalla et al. 2010; Neef et al. 2010) that may elicit regenerative, spontaneous waves of Ca^{2+} release causing aftercontractions, transient inward current (I_{Ti}), and DADs (Fujiwara et al. 2008; Curran et al. 2010). CaMKII expression and activity is increased in the failing heart (Kirchhefer et al. 1999; Hoch et al. 1999; Ai et al. 2005; Sossalla et al. 2010; Anderson et al. 2011). Inhibition of CaMKII activity was shown to abolish isoproterenol-induced spontaneous Ca^{2+} waves and DADs in ventricular myocytes isolated from failing rabbit (Curran et al. 2010) and mouse (Sag et al. 2009) hearts, to decrease I_{Kr}-block-induced EADs in rabbit heart (Anderson et al. 1998), and to improve contractile function and reduce the leak of Ca^{2+} from the sarcoplasmic reticulum in myocytes from failing human hearts (Sossalla et al. 2010). Atrial fibrillation has been associated with increases of both late I_{Na} and CaMKII activity (Benito et al. 2008; Neef et al. 2010; Hove-Madsen et al. 2004).

The positive feedback loop between late I_{Na} and CaMKII activation is completed by a CaMKII-mediated increase of late I_{Na} (Maltsev et al. 2008; Wagner et al. 2006, 2011; Aiba et al. 2010; Ma et al. 2012). CaMKII associates with and phosphorylates the Na^+ channel (Hund et al. 2010; Wagner et al. 2006). Inhibition of CaMKII has been shown to reduce both contractile dysfunction and late I_{Na} in guinea pig isolated hearts and myocytes exposed to ouabain (Hoyer et al. 2011), and inhibition of late I_{Na} was shown to reduce arrhythmic activity and a rapid pacing-induced increase of diastolic tension in papillary muscles isolated from mice overexpressing CaMKIIδ_C (Sossalla et al. 2011). The late I_{Na} inhibitor ranolazine decreases phosphorylation of CaMKII, RyR2, and phospholamban in N1325S mouse hearts (Yao et al. 2011). Thus, the feedback loop between the amplitude of late I_{Na} and CaMKII activity can be interrupted using inhibitors of CaMKII or late I_{Na}, either of which can reduce EADs and DAD incidence, dispersion of repolarization, Ca^{2+} alternans, and diastolic contracture. Finally, during the development of cardiac hypertrophy and failure, CaMKII appears to have an important role in the regulation of cardiac gene transcription (Zhang et al. 2007; Backs et al. 2009). Sodium channel expression is decreased in the failing heart (Undrovinas et al. 2002; Zicha et al. 2004), but evidence linking transcriptional control of *SCN5A* by CaMKII is lacking.

6.4 Role of Late I_{Na} in Dispersion of Repolarization and Related Arrhythmias

Reentrant arrhythmias generally involve unidirectional block and conduction around a circuit long enough to enable recovery of excitability at each point in the circuit before the circus wave of excitation returns (Mines 1914). The length of the circuit must be greater than the distance that an impulse can travel (i.e., the wavelength, a product of conduction velocity, and refractory period) before reaching the same point again. The establishment of unidirectional block is facilitated by an increase in dispersion of repolarization associated with both acquired or congenital conditions that prolong or abbreviate AP duration and the QT interval, thus promoting the substrate for reentry (Di Diego and Antzelevitch 1993; Antzelevitch 2007, 2008; Patel and Antzelevitch 2008a; Galinier et al. 1998; Yan et al. 2001; Sicouri et al. 2010; Benoist et al. 2012). Computational modeling studies also indicate that increased AP dispersion and weaker cell-to-cell coupling is associated with the susceptibility to reentrant arrhythmic activity (Ghanem et al. 2001; Burnes et al. 2001).

Preferential abbreviation of AP duration and refractoriness in epicardium vs. endocardium under short QT and Brugada syndrome conditions can also provide the substrate for reentry, both in atria and ventricles (Antzelevitch 2008; Sicouri et al. 2010; Antzelevitch and Sicouri 2012; Nof et al. 2010; Fish and Antzelevitch 2008; Patel and Antzelevitch 2008b). Acute ischemia also contributes to induction of reentry by causing electrical heterogeneity and conduction block (Vermeulen et al. 1996; Sidorov et al. 2011).

In normal hearts, late I_{Na} is greater in Purkinje fibers and M cells than in endo- or epicardial cells, thereby contributing to the longer duration of the AP in these cells (Zygmunt et al. 2001; Coraboeuf et al. 1979) and to spatial dispersion of AP duration and refractoriness. Block of late I_{Na} reduces AP duration in Purkinje fibers and M cells and is associated with reduction of the transmural dispersion of AP duration. (Sicouri et al. 1997a, b; Shimizu and Antzelevitch 1997b; Antzelevitch and Oliva 2006; Antzelevitch et al. 2006) Augmented late

I_{Na} likely contributes to arrhythmogenesis in failing hearts due to increase in dispersion of repolarization and repolarization variability secondary to the increase in late I_{Na} (Maltsev et al. 2007). Reduction of late I_{Na} is effective in abbreviating APD and repolarization variability (Undrovinas et al. 2006). Late I_{Na} enhancers, including anthopleurin-A and veratridine increase the dispersion of AP duration in intact isolated guinea pig and rabbit hearts, respectively (Restivo et al. 2004; Milberg et al. 2005). Augmentation of late I_{Na} with ATX-II has been shown to dramatically increase transmural dispersion of repolarization and refractoriness in canine left ventricular wedge preparations, giving rise to TdP (Shimizu and Antzelevitch 1997a, b).

Inhibition of late I_{Na} whether by mexiletine, ranolazine, or other agents reverses the effect of the late I_{Na} enhancers, effectively reducing spatial dispersion of repolarization and refractoriness, thus suppressing TdP (Wu et al. 2004; Shimizu and Antzelevitch 1997b, 1998, 1999a, b; Wu et al. 2003). Figure 3 illustrates the effect of I_{Kr} and I_{Ks} blockers as well as a late I_{Na} agonist to promote transmural dispersion of repolarization (TDR) and prolonged Tpeak–Tend intervals in the ECG by producing a preferential prolongation of the M cell action potential duration. Block of late I_{Na} with mexiletine reduces TDR in these experimental models of long QT 1, 2, and 3. Reduction of late I_{Na} can also reduce spatial dispersion of repolarization and beat-to-beat variability of repolarization caused by treatment of rabbit isolated hearts with the I_{Kr} blocker, E-4031 (Wu et al. 2009b). Taken together, these results support the view that either reduction of repolarizing K^+ current or enhancement of late I_{Na} results in increased dispersion of repolarization that may lead to arrhythmias and that reduction of late I_{Na} is effective is reversing these proarrhythmic effects (Fig. 4).

6.5 Role of Late I_{Na} in Cardiomyopathy

As discussed above, acquired and congenital defects that augment late I_{Na} do so by varied molecular mechanisms, including sodium channel phosphorylation, mutations of a specific amino acid residue(s) in the α or β subunits, or by alteration of channel-interacting proteins, which may promote varied phenotypes. In addition to congenital and acquired LQTS, an increase in late I_{Na} can result in mechanical dysfunction of the heart. Dilated cardiomyopathy has been reported in patients (McNair et al. 2004) as well as in mice (Zhang et al. 2011) with mutations in *SCN5A* associated with a gain of function in late I_{Na}. Mechanical dysfunction can result from an increase of intracellular Na^+ to decrease the electrochemical gradient for Ca^{2+} extrusion by Na^+–Ca^{2+} exchange (Belardinelli et al. 2006; Noble and Noble 2006; Sossalla et al. 2008). Slowing of Ca^{2+} extrusion could lead to slowing of diastolic relaxation. It is noteworthy that patients expressing the LQT3-ΔKPQ mutant Na^+ channel are reported to have an impaired diastolic left ventricular relaxation and AP prolongation that were improved after administration of ranolazine (Moss et al. 2008).

Hypertrophic cardiomyopathy (HCM) is the most common monogenic cardiac disorder encountered in the clinic. Recent studies have identified the presence of cells with M cell characteristics in the septum of the human heart, (Barajas-Martinez et al. 2013; Coppini et al. 2013) as has previously been described in the canine heart (Glass et al. 2007; Sicouri et al. 1994) displaying higher levels of late I_{Na}. An ameliorative effect of ranolazine was

shown to reduce the augmented late I_{Na} and thus to reduce the prolonged APD in the setting of HCM.

Coppini et al. (2013) showed that in cardiomyocytes isolated from HCM, enhanced CaMKII activity slows ICa inactivation and increases late I_{Na}, thus contributing to APD prolongation and related arrhythmias. Their data also suggested that by altering the function of EC-coupling proteins, CaMKII might also contribute to the altered Ca^{2+}-transient kinetics and elevation of diastolic $[Ca^{2+}]i$, which are responsible for the development of delayed afterdepolarizations (DAD). Therapeutic concentrations of ranolazine partially reversed the HCM-related cellular abnormalities via inhibition of late I_{Na}, with negligible effects in myocytes isolated from control hearts.

7 Drugs That Inhibit Cardiac Late I_{Na}

Local anesthetic and antiarrhythmic agents, including mexiletine, lidocaine, ranolazine, amiodarone, propranolol, verapamil, pentobarbital, quinidine, and flecainide, as well as antiepileptic drugs such as phenytoin and riluzole, are known to inhibit late I_{Na} in cardiac myocytes. These drugs lack selectivity for inhibition of late I_{Na} relative to other currents or receptor targets (Table 2). TTX is a selective Na^+ channel blocker (Narahashi 2008) that inhibits late I_{Na} in the heart at concentrations 5–10-fold lower than it inhibits peak I_{Na} (Carmeliet 1987a; Wu et al. 2009a; Le Grand et al. 1995; Josephson and Sperelakis 1989) and it is commonly used in experiments to validate the effects of other late I_{Na} blockers. However, TTX blocks neuronal Na^+ channels at much lower concentrations than those at which cardiac $Na_V1.5$ channels are blocked, accounting for its high toxicity.

The antianginal drug ranolazine (Antzelevitch et al. 2011), GS-458967 (Belardinelli et al. 2013), and the Pierre Fabre experimental compound F15845 (Vacher et al. 2009) appear to be the most selective inhibitors of cardiac late I_{Na} reported to date. Ranolazine has been demonstrated to be safe (Morrow 2007) in patients with non-ST-elevation acute coronary syndromes and angina pectoris. Ranolazine inhibits late I_{Na} and I_{Kr} with potencies of 6 and 12–14 μmol/L, respectively, (Antzelevitch et al. 2004) and slightly prolongs the QT interval in humans (Chaitman 2006). It also blocks both α- and β-adrenergic receptors with low potency (Zhao et al. 2011).

Most drugs that selectively inhibit cardiac late I_{Na} are believed to bind to the local anesthetic site in the $Na_v1.5$ Na^+ channel vestibule, and they cause both useand voltage-dependent block of the Na^+ current (Zygmunt et al. 2011; Nesterenko et al. 2011). Local anesthetic binding to the Na^+ channel is state dependent, and high-affinity binding depends on the availability of a channel conformation in which certain amino acids are arranged in a specific 3D relationship to form a binding domain (Lipkind and Fozzard 2005). In any different conformation (e.g., the closed state), the same amino acids are present but in different relative 3D positions that do not form a local anesthetic binding site of high affinity. The amino acids that form the putative local anesthetic site in open/inactivated Na^+ channel include F1759 and Y1766 (F1760 and Y1767 in hH1) in DIVS6, but much data indicate that other amino acids contribute to local anesthetic binding, and more than one binding site may be present [for review, see Mike and Lukacs (2010)]. It should be noted

that the binding site for batrachotoxin in the Na^+ channel vestibule overlaps that for local anesthetics (however, at a molecular weight of 539, batrachotoxin is larger than most local anesthetics) and displacement of its binding has been used to identify potential use-dependent Na^+ channel blockers (Carter et al. 2000; Grauert et al. 2002).

The antiarrhythmic effects of drugs and agents that reduce late I_{Na} have been demonstrated by many investigators using many different cardiac preparations (e.g., (Antzelevitch et al. 2004, 2011; Ruan et al. 2009; Undrovinas et al. 1999; Wu et al. 2004; Sicouri et al. 1997a; Scirica et al. 2007; Antzelevitch and Belardinelli 2006; Song et al. 2004; Sheu and Lederer 1985; Fedida et al. 2006; Burashnikov et al. 2007; Pignier et al. 2010)). In these studies, late I_{Na} is enhanced as a result of disease (e.g., heart failure), ischemia or hypoxia, gain-of-function mutations in *SCN5A*, or application of toxins (e.g., ATX-II, veratridine, aconitine), intermediary metabolites (e.g., palmitoyl-L-carnitine), or H_2O_2. Inhibition of late I_{Na} has been shown to improve function and reduce arrhythmogenic activity in ventricular, atrial, pulmonary vein sleeve, and nodal cardiac tissues. Diastolic depolarization, triggered activity (EADs, DADs), AP duration and variability, and cytosolic concentrations of Na^+ and Ca^{2+} are reduced following inhibition of a pathologically enhanced late I_{Na}. Reduction of late I_{Na} increases repolarization reserve (shortens AP duration) and attenuates the proarrhythmic effects of I_{Kr} blockers. Spontaneous and pause-triggered arrhythmic activity (i.e., *TdP*) induced by amiodarone, quinidine, moxifloxacin, cisapride, and ziprasidone in the female rabbit isolated heart is reduced by the late I_{Na} inhibitor ranolazine (Wu et al. 2006, 2008b, c). In the dog heart, inhibition of late I_{Na} reduces AP duration more in myocytes with longer AP durations (Purkinje fibers and M cells) than in myocytes with short AP duration (epicardial cells) and thus decreases the transmural dispersion of repolarization (Antzelevitch and Belardinelli 2006; Shimizu and Antzelevitch 1997b). No risks associated with the block of cardiac late I_{Na} have been identified to date.

GS-458967, a recently introduced Gilead Sciences compound, is a selective late I_{Na} inhibitor with an IC_{50} of 200 nM. The compound was shown to cause modest abbreviation of APD and to prevent or abolish both ATX-II and E-4031-induced (i.e., models of LQT3 and LQT2, respectively) ventricular tachycardias in rabbit hearts (Belardinelli et al. 2013). Other recent studies have also demonstrated the effect of GS-458967 to abolish EADs and EAD-induced triggered activity elicited by exposure of canine Purkinje fibers to ATX-II (Fig. 5), increased extracellular calcium, and isoproterenol (Sicouri et al. 2013). GS-458967 may be useful to confirm the pathologic roles of late I_{Na} and to investigate physiologic and pathologic effects of inhibiting late I_{Na} in other excitable tissues.

Conclusion

Evidence implicating enhancement of late I_{Na} in pathophysiological electrical and mechanical instabilities of the heart is steadily increasing (Fig. 6). Selective inhibition of late I_{Na} is expected to be an effective strategy for correcting these channelopathies and cardiomyopathies. Unlike most other antiarrhythmic drugs, selective inhibitors of late I_{Na} do not appear to be proarrhythmic. Future direction focused on development of highly selective late I_{Na} blockers are needed to test this hypothesis in the clinic.

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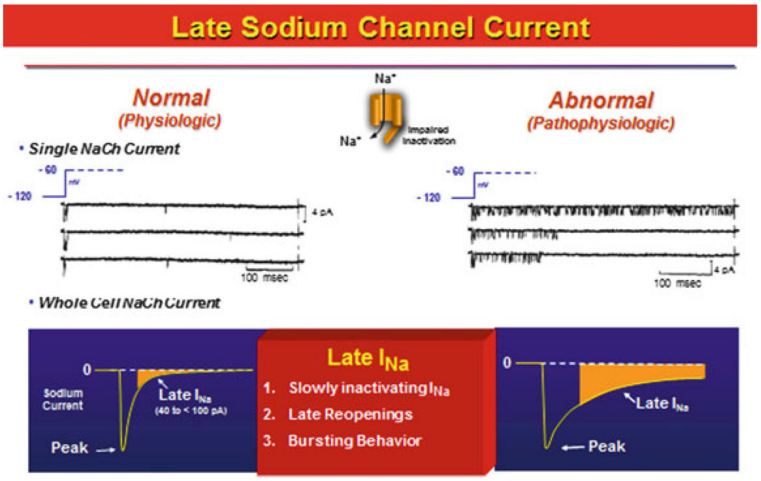

Fig. 1.

Late sodium channel current is the current flowing during the plateau of the cardiac action potential and is comprised of slowly inactivating sodium channel current, late re-openings, and bursting behavior of the sodium channels. Modified from Belardinelli et al. (2004), with permission

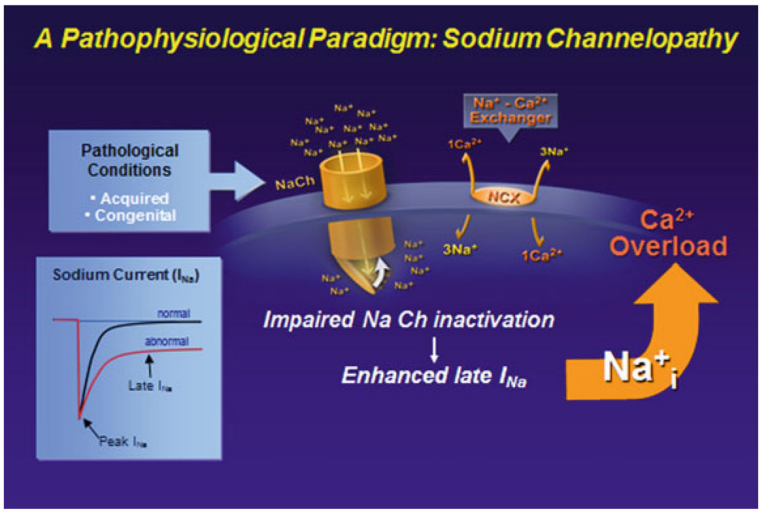

Fig. 2.

The pathophysiological paradigm for enhanced late I_{Na}. In both acquired and congenital syndromes, impaired inactivation of the sodium channel leads to enhanced late I_{Na}, causing a rise in intracellular Na concentration, which leads to calcium overload conditions. Modified from Belardinelli et al. (2006), with permission

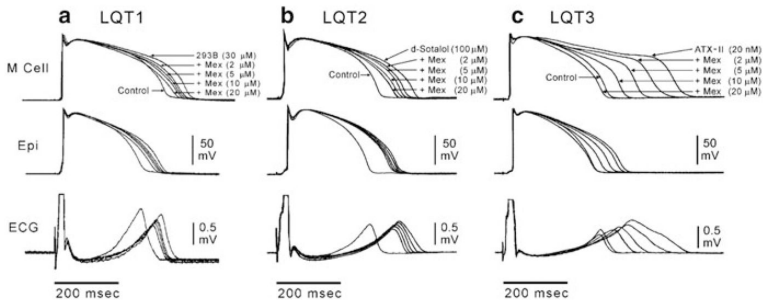

Fig. 3.

I_{Kr} and I_{Ks} blockers and Late I_{Na} agonist promote transmural dispersion (TDR) of repolarization and prolonged Tpeak–Tend intervals in the ECG by producing a preferential prolongation of the M cell action potential duration. Block of late I_{Na} with mexiletine reduces TDR in these experimental models of the long QT syndrome. Each panel shows transmembrane action potentials recorded from M and epicardial (Epi) sites in canine left ventricular wedge preparations together with a transmural ECG recorded across the bath (BCL of 2,000 ms). Traces are recorded in the presence of the I_{Ks} blocker, chromanol 293B (LQT1), I_{Kr} blocker D-sotalol (LQT2), and late I_{Na} agonist, ATX-II (LQT3), plus increasing concentrations of mexiletine. Mexiletine produced a greater abbreviation of the M cell vs. epicardial action potential at every concentration, resulting in a reduction in transmural dispersion of repolarization in all three LQTS models. Modified from (Shimizu and Antzelevitch 1997b, 1998) with permission

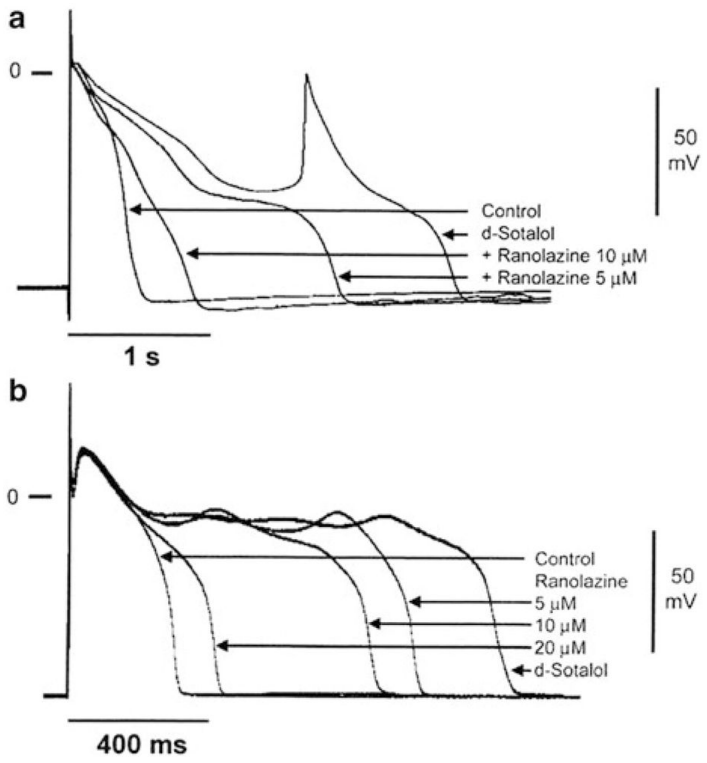

Fig. 4.

Effect of ranolazine to suppress D-sotalol-induced action potential prolongation and early afterdepolarizations in Purkinje fiber (**a**) and M cell preparations (**b**). Modified from Antzelevitch et al. (2004)

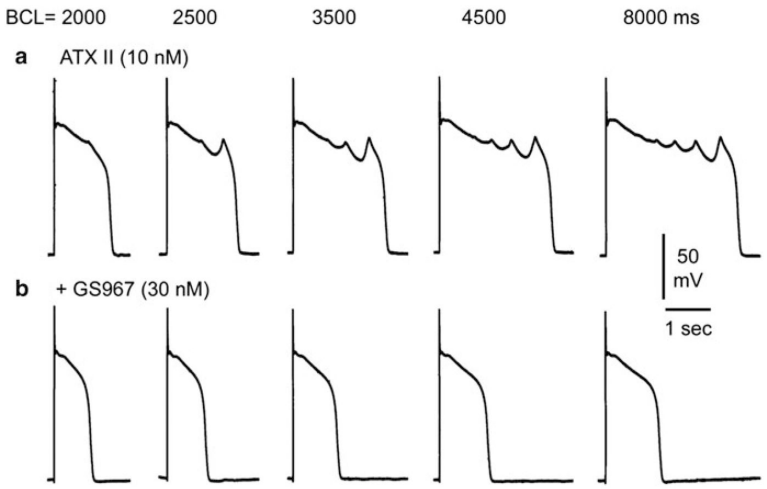

Fig. 5.

GS-458967 abolishes early afterdepolarizations (EADs) and EAD-induced triggered activity elicited by exposure to ATX-II in a canine Purkinje fiber. (**a**) ATX-II (10 nM) elicited EADs and EAD-induced triggered activity at basic cycle lengths (BCLs) of 2,000, 2,500, 3,500, 4,500, and 8,000 ms. GS-458967 (30 nM) abolished all EADs and triggered activity. From Sicouri et al. (2013) with permission

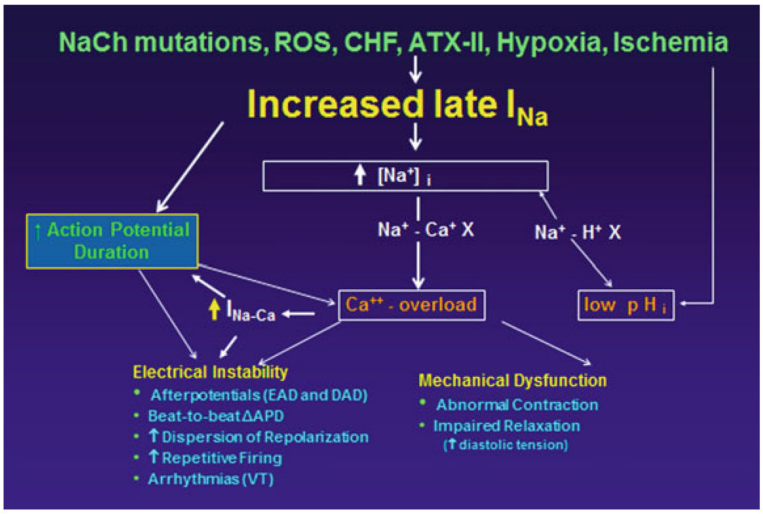

Fig. 6.

Mechanisms contributing to electrical instability and mechanical dysfunction in acquired and congenital conditions that enhance late I_{Na}

Table 1

Conditions and agents that have been demonstrated to increase cardiac late I_{Na}

Conditions/endogenous agents	Drugs and toxins
Activation of CaMKII	Aconitine
Activation of Fyn tyrosine kinase	ATX-II
Activation of PKC	Batrachotoxin
Angiotensin II	DPI 201–106 and analogs
Carbon monoxide	KB130015
2,3-Diphosphoglycerate	Ouabain (indirectly)
Hydrogen peroxide (H_2O_2)	Pyrethroids (e.g., tefluthrin)
Hypoxia, ischemia Hyperthyroxinemia	Veratridine
Lysophosphatidylcholine	
Nitric oxide (NO)	
Palmitoyl-L-carnitine	

Modified from Shryock et al. (2013), with permission

Table 2

IC_{50} values for drug-induced block of peak and late I_{Na} as well as I_{Kr} by I_{Na} blockers

		IC_{50} value for tonic block (μM)			
Drug	**MW**	**Late I_{Na}**	**Peak I_{Na}**	**hERG (I_{Kr})**	**References**
Amiodarone (acute)	645	3.0, 6.7	178, 87	~ 1	Wu et al. (2008c), Maltsev et al. (2001)
Flecainide	414	1.4	10–15	2.1, 3.9	Liu et al. (2003), Heath et al. (2011)
F15845	376	~1	23 % at 10 μM	15 % at 10 μM	Vacher et al. (2009), Pignier et al. (2010)
GS458967	347	0.2	>10	>10	Sicouri et al. (2012c)
KC12291	413	≤10	~15	No inhibition?	Tamareille et al. (2002), John et al. (2004)
Lidocaine	236	~25	~300	No inhibition	Bean et al. (1983), Grant et al. (1989), Starmer et al. (1991)
Mexiletine	179	3–5	28–253	No inhibition	Yatani and Akaike (1985), Sunami et al. (1993)
Propafenone	341	<1	≥1	0.4–0.8	Schreibmayer and Lindner (1992), Edrich et al. (2005), Witchel et al. (2004)
Propranolol	259	~3	22–28	No inhibition	Wang et al. (2008, 2010)
Quinidine	324	12	11	~1	Colatsky (1982), Grant et al. (1982)
R56865	413	0.2	~5	Probable inhibition	Wilhelm et al. (1991), Verdonck et al. (1991)
Ranolazine	428	7	428	12–14	Antzelevitch et al. (2004), Zygmunt et al. (2011), Undrovinas et al. (2004)
Riluzole	234	2.7–3	100–150		Song et al. (1997), Weiss et al. (2010)
Tetrodotoxin	319	0.53	6.0	No inhibition	Josephson and Sperelakis (1989), Carmeliet (1987b)
Vernakalant	349	~30	107	7–21	Orth et al. (2006), Fedida (2007)