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Inhibition of Late Sodium Current as an Innovative Antiarrhythmic Strategy

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Abstract
Purpose of review Over the last years, evidence is accumulating that enhanced late sodium current (I_{NaL}) in cardiac pathologies has fundamental consequences for cellular electrophysiology. This review discusses the underlying mechanisms of I_{NaL}-induced arrhythmias and the significance of I_{NaL}-inhibition as a possible therapeutic approach.
Recent Findings Inhibition of enhanced I_{NaL}, e.g., by ranolazine, was shown to reverse these effects in different myocardial diseases including heart failure. The antianginal drug ranolazine has already been examined in larger clinical trials with promising antiarrhythmic actions.
Summary Enhanced I_{NaL} was found to be present in several cardiac pathologies like ischemia, long QT syndromes, hypertrophic cardiomyopathy, and heart failure. In settings of enhanced I_{NaL}, a sodium-dependent calcium overload leads to severe impairment of excitation-contraction coupling and therefore has a high proarrhythmogenic potential. Experimental data showed that inhibition of I_{NaL} has a high antiarrhythmic potential which could be confirmed in further clinical trials.

Keywords Late sodium current · Heart failure · Arrhythmia · Ranolazine · Remodeling

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Background

Heart failure constitutes one of the major causes for morbidity and mortality within the western world. Approximately 1–2% of the population is affected and prevalence dramatically increases after the age of 70. Therefore, heart failure represents a major burden for public health in an aging population [1]. Up to 50% of these heart failure patients die from arrhythmias and sudden cardiac death. However, pharmacological antiarrhythmic therapy of those patients is limited or inefficient [2].

The underlying causes for these arrhythmias are complex structural and electrical remodeling processes in response to myocardial injury. Electrical remodeling has been linked to development of atrial fibrillation and potentially lethal ventricular arrhythmias. Major determinants of electrical remodeling in heart failure involve alteration of numerous ion channels and disturbed intracellular Ca^{2+} cycling. A major issue of electrical remodeling in heart failure is prolongation of the action potential (AP) with possible occurrence of early afterdepolarizations (EADs).

A complex interplay between different ion currents is involved in remodeling of the cardiac AP. This includes outward K^+ currents (I_k), inward Ca^{2+} currents (I_{Ca}), and a persistent component of the inward Na^+ currents (I_{Na}). Additionally, altered current densities and changes in the spatial distribution of I_K, I_{Ca}, and I_{Na} occur in the presence of heart failure [3]. An important role in AP prolongation and arrhythmias is attributed to the persistent or late component of the inward Na^+-current (I_{NaL}) [4–9].

The Late Sodium Current

Cardiac excitation depends on highly and well-coordinated voltage-gated sodium channels (Na_V) that generate the AP

upstroke [10, 11]. Na_V are inactivated as quickly as they are activated which is required for cell membrane repolarization and electrical stability. While voltage-dependent inactivation readily switches off most of Na_V (I_{Na}) current, a small portion of persistent (late) sodium current (I_{NaL}) is present even in physiological conditions [4]. A direct link is established between augmented I_{NaL} and increased vulnerability for arrhythmias [5]. Many studies have provided evidence that I_{NaL} is increased in heart failure which subsequently leads to AP prolongation and arrhythmias [4–7]. Moreover, I_{NaL} is enhanced in several other pathophysiological conditions such as hypertrophy, ischemia, and atrial fibrillation (Fig. 1) [8, 12–15].

Despite plenty of research has been done on I_{NaL}, there still is limited knowledge about the underlying mechanisms of I_{NaL} augmentation in cardiac pathologies. As some of the neuronal sodium channels were additionally shown to be expressed in the heart, defining the origin of I_{NaL} augmentation even got more complicated [16].

Cardiac Sodium Channels

The "cardiac" sodium channel $Na_V1.5$ is encoded by the *SCN5A* gene and is expressed as the primary cardiac sodium channel in all excitable tissue in the heart. Several different proteins have been identified regulating expression and function of the channel [17]. Malfunctions of $Na_V1.5$ whether congenital or acquired are associated with cardiac disorders and arrhythmias. Mutations in the *SCN5A* gene have been linked to congenital arrhythmias like long QT syndrome type 3 and Brugada syndrome [18]. Moreover, regulation of the channel is changed under pathological conditions as already mentioned above. Regulatory changes are caused by altered post-translational modifications through associated proteins that modulate biophysical function of the channel [19, 20]. In this case, a major role is attributed to Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) which is one of the key players in cardiac pathophysiology. The predominant cardiac isoform CaMKIIδ was also described to slow the fast inactivation of inward sodium current [6, 21]. Phosphorylation by CaMKII and other kinases is known to shift voltage dependence of current activation and inactivation as well as a negative shift of channel availability [22, 23]. All these mechanisms could contribute to increased I_{NaL} via $Na_V1.5$. Furthermore, different phosphorylation sites for CaMKIIδ and other kinases at $Na_V1.5$ have been identified [24, 25].

$Na_V1.5$ early became a target of antiarrhythmic therapy. Vaughn-Williams divided sodium channel inhibitors in three classes (Ia, Ib, Ic), which differ regarding their effects on action potential duration (APD) and effective refractory period [26]. The CAST Study evaluated the potential of reducing sudden cardiac death by Na_V inhibition in patients after myocardial infarction. However, the study was canceled after 10 months because of increased mortality compared to placebo. That is why class I antiarrhythmics and most other antiarrhythmic drugs apart from amiodarone are contraindicated in patients with significant structural heart disease now [27, 28]. Therefore, a major group of patients that require antiarrhythmic treatment have limited therapeutic options. Most importantly, the majority of these patients need longer or lifelong antiarrhythmic treatment with these compounds. This raises the need for novel antiarrhythmic strategies that act more specific, e.g., via I_{NaL} and do not affect cardiac conduction by inhibiting the peak sodium current ($I_{Na,peak}$).

Non-cardiac Sodium Channels

Studies showing an association of electrocardiographic (ECG) abnormalities with epilepsy [29] and myotonic disorders [30] lead to the idea that mutated non-cardiac sodium channels might also cause electrophysiological disturbances in the heart. These non-cardiac sodium channel isoforms were later identified in cardiac tissue [16, 31, 32].

Some studies suggested that non-cardiac Na_V may contribute to I_{NaL} augmentation. A report by Biet et al. showed a significant (~50%) contribution to I_{NaL} by non-cardiac Na_V isoforms in healthy canine cardiomyocytes [32]. In another study, Xi et al. proposed that an increased I_{NaL} may be explained by overexpression of neuronal $Na_V1.1$ and $Na_V1.6$ in a rat HF model [9]. Another group suggested a relevant contribution of $Na_V1.1$ to I_{NaL} in a dog HF model [33].

In recent years, the neuronal sodium channel $Na_V1.8$ was also proposed to contribute to I_{NaL} in cardiomyocytes as it was shown to be expressed in mouse hearts [34]. Moreover, expression in intracardiac neurons [35] and human heart tissue was demonstrated [36]. Furthermore, genome-wide association studies (GWAS) have reported that single nucleotide polymorphisms in the *SCN10A* gene, which encodes $Na_V1.8$, are associated with modulation of cardiac conduction, as well as heart rate and arrhythmic risk [37–39].

Interestingly, Yang et al. showed that A-803467, a specific blocker of $Na_V1.8$, can selectively block I_{NaL} in rabbit and mouse ventricular cardiomyocytes and, therefore, shortens the APD without any impact on $I_{Na,peak}$ [34]. A recent study reported discovery of a novel selective and orally bioavailable $Na_V1.8$ blocker PF-01247324 which modulates augmented I_{NaL} in sensory neurons [40]. Moreover, different studies reported that $Na_V1.8$ significantly contributes to I_{NaL} triggers and arrhythmogenesis. A recent study showed coding sequence variations in the *SCN10A* gene to be associated with vulnerability to atrial fibrillation. Electrophysiological studies showed increased I_{NaL} for most of the variants [41]. Therefore, novel physiological blockers specifically targeting $Na_V1.8$ may be an interesting therapeutic option for experimental treatment of arrhythmias.

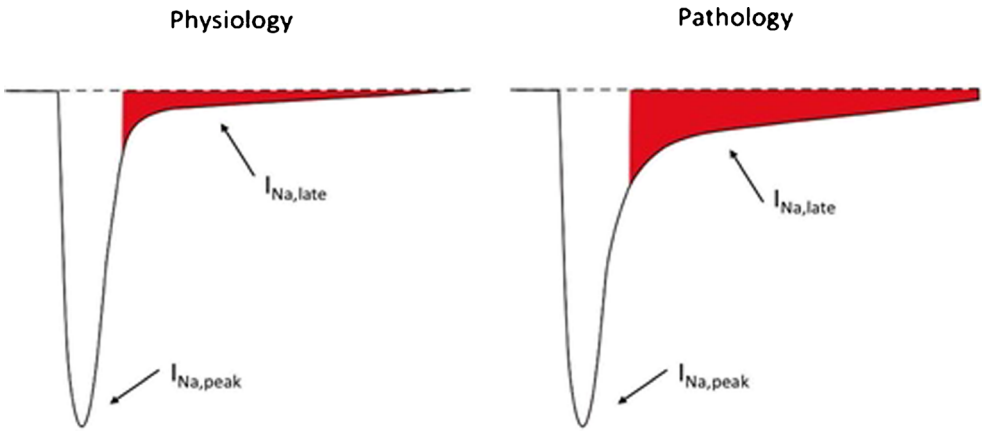

Fig. 1 Inward sodium current can be divided into a peak and a late component; both components are also present under physiologic conditions; late sodium current is known to be enhanced in cardiac pathology

These findings on non-cardiac sodium channels lead to the consideration that inhibition of these channels could provide an approach targeting I_{NaL} without affecting $I_{Na,peak}$. by influencing $Na_V1.5$.

Proarrhythmogenic-Enhanced Late Sodium Current

According to current knowledge, augmented I_{NaL} is part of an ongoing vicious circle in cardiac pathology. Especially I_{NaL} in relation to CaMKII constitutes a key player of cardiac disease [42], which makes it an important issue. CaMKII is known to phosphorylate several ion channels and other proteins involved in excitation-contraction coupling [43]. Furthermore, it was shown to be activated in several pathological conditions of the myocardium [44]. As mentioned before, phosphorylation by CaMKII affects kinetics of the cardiac sodium channel $Na_V1.5$ [21, 24, 25]. This enhances the I_{NaL} and therefore increases intracellular sodium ($[Na]_i$). As a consequence, reverse mode of Na^+/Ca^{2+} exchanger (NCX) is activated causing enhanced Ca^{2+} influx [45]. Elevated intracellular calcium ($[Ca^{2+}]_i$) subsequently activates both ryanodine receptors (RyR2) and CaMKII. CaMKII further phosphorylates RyR2, leading to diastolic Ca^{2+} leak [46], and $Na_V1.5$, stimulating the cycle again. Elevated diastolic Ca^{2+} is extruded by forward mode of NCX, generating an inward sodium current again.

Increased inward sodium currents during the action potential plateau and prolonged APD result in early afterdepolarizations (EADs) [47]. Diastolic Ca^{2+} extrusion via NCX can generate a depolarizing current leading to delayed afterdepolarizations (DADs) [48]. Both EADs and DADs can result in life-threatening arrhythmias (Fig. 2).

As CaMKII regulates various proteins in intracellular myocardial signaling, it represents an unspecific target for a therapeutic antiarrhythmic approach. Additionally, by now, there is no clinical substance known to inhibit CaMKII specifically in cardiac tissue. Therefore, inhibiting augmented I_{NaL} might constitute the most reasonable target to break the vicious circle.

Therapeutic Inhibition of I_{NaL}

As an enhanced I_{NaL} was found in several cardiac pathologies, it became an interesting target for pharmacological inhibition. Over the last years, new agents inhibiting I_{NaL} were discovered and established drugs were studied for their detailed effects on I_{NaL}. Class I antiarrhythmics such as lidocaine and flecainide were shown to have inhibitory effects on I_{NaL}, as well as class III antiarrhythmic amiodarone [49]. However, these compounds were not selective enough for I_{NaL} compared to $I_{Na,peak}$.

The best examined clinically approved compound inhibiting I_{NaL} is ranolazine, which was primarily released as an anti-ischemic drug. Later, ranolazine was found to inhibit I_{NaL} potently up to 38-fold higher than $I_{Na,peak}$ [50, 51]. Several experimental studies showed ranolazine to reduce $[Na]_i$, thereby NCX reverse mode and diastolic Ca^{2+} overload in heart failure, ischemia, and oxidative stress [6, 52, 53].

In myocardial trabeculae from human end-stage failing hearts, ranolazine reduced the excessive increase in diastolic tension [54]. In papillary muscles of transgenic CaMKII-overexpressing mice, it also attenuates diastolic dysfunction [55]. Similar results were found by Coppini et al. in isolated ventricular myocytes and trabeculae from patients with hypertrophic cardiomyopathy. Treatment with ranolazine resulted in a faster kinetics of the Ca^{2+} transients and lower diastolic Ca^{2+}. Both resulting in an accelerated contraction-relaxation cycle and therefore improved diastolic function [8]. Further experimental in vivo studies demonstrated reduced left ventricular end-diastolic pressure and increased left ventricular ejection fraction and stroke volume after acute infusion with ranolazine in a canine heart failure model [56]. A first proof-of-concept study to evaluate the effects of ranolazine in diastolic heart failure was the RALI-DHF study. It showed a significant decrease in left ventricular end-diastolic pressure 30 min after infusion of ranolazine. However, relaxation parameters measured by echocardiography were unchanged [57]. In this context, newer experimental data from Coppini et al. should be mentioned. They showed that I_{NaL} inhibition

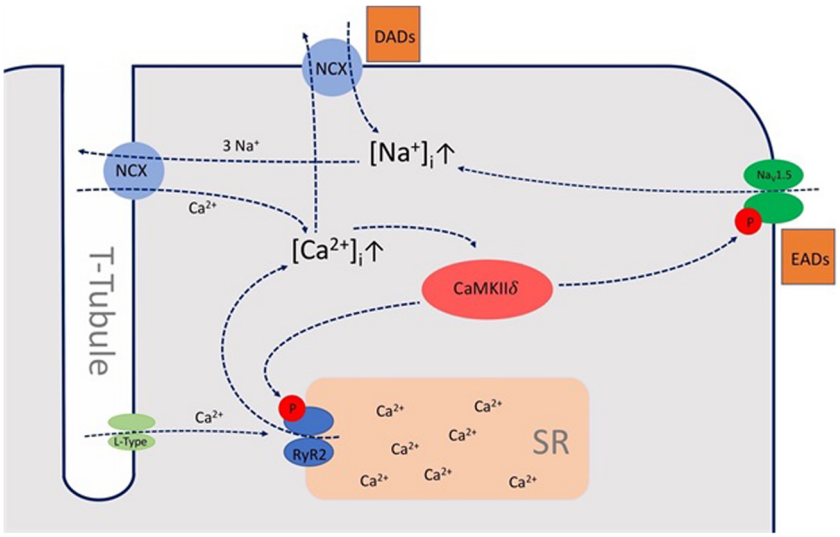

Fig. 2 Vicious circle of increased late sodium current in cardiac pathology; sodium-dependent calcium overload triggers Ca^{2+}/calmodulin-dependent protein kinase II activity, and enhanced inward sodium current results in action potential prolongations and early afterdepolarizations due to sodium overload; increased diastolic calcium is extruded via NCX causing a depolarizing inward sodium current with potential delayed afterdepolarizations; increased Ca^{2+}/calmodulin-dependent protein kinase II activity actuates the vicious circle again

with ranolazine prevented the phenotype development in a mouse model of hypertrophic cardiomyopathy [58].

An enhanced I_{NaL} is potentially involved in arrhythmogenesis by changing cellular electrophysiology. Therefore, different compounds were tested regarding their potential to selectively inhibit this current. Tetrodotoxin (TTX) is historically known to inhibit the cardiac sodium channel isoform $Na_V1.5$. Maltsev et al. showed that application of 10 μmol/L of TTX not only reversibly blocked I_{NaL} but also abbreviate APD and suppressed EADs in cardiomyocytes from human failing hearts [4]. As mentioned before, ranolazine was also found to inhibit I_{NaL} in cardiomyocytes, thereby suppressing EADs in a model of long QT syndrome [59]. Further research examined the antiarrhythmic effects of I_{NaL} inhibitors in settings of pharmacologically enhanced I_{NaL}. A potent inducer of I_{NaL} is sea anemone toxin (ATX-II) which consequently induces APD prolongation, EADs, and DADs in different experimental settings [54, 60]. In the light of this, it was demonstrated that ATX-II-induced effects on APD, EADs, and I_{NaL} could be reduced by both TTX [4] and ranolazine [59]. Increased CaMKII expression was shown to enhance I_{NaL} by direct interaction with the cardiac sodium channel. In a model with transgenic overexpressed CaMKII activity where I_{NaL} was enhanced, CaMKII-inhibition could prevent I_{NaL} enhancement and in further consequence APD prolongation and arrhythmias [21]. In the same model, later I_{NaL} inhibition by ranolazine was also shown to reduce arrhythmias significantly [61]. I_{NaL} inhibition by TTX or ranolazine was also shown to act as antiarrhythmic in pathological conditions of enhanced I_{NaL}. Our group could demonstrate that ranolazine and TTX normalize enhanced I_{NaL} in a model of pressure-induced heart failure. Accordingly, APD was abbreviated by both drugs [6]. Similar results could be observed by Coppini et al. in isolated ventricular cardiomyocytes from patients with hypertrophic cardiomyopathy indicating the significant contribution of I_{NaL} to APD prolongation and electrical instability in the failing heart [8].

A second mechanism of I_{NaL} contributing to proarrhythmia is the formation of DADs. These arrhythmogenic triggers result from sodium-dependent calcium overload, which is caused by reverse mode of NCX due to elevated Na^+ concentration and prolonged APD. This diastolic Ca^{2+} overload also causes CaMKII activation and thereby as a consequence RyR2-phosphorylation diastolic Ca^{2+} leak of the sarcoplasmic reticulum also in the human heart [55, 62, 63]. Inhibition of either CaMKII or I_{NaL} was shown to reduce diastolic SR-Ca^{2+} leak and to suppress the occurrence of DADs [6, 62, 64]. As DADs appear to be Ca^{2+} dependent, Song and coworkers nicely demonstrated the RyR dependence of I_{NaL}-induced arrhythmias [48]. They showed ranolazine to prevent APD prolongation and EADs as well as DADs after induction of I_{NaL} with ATX-II [48]. Further, they used the sarcoplasmic reticulum Ca^{2+}-release channel inhibitor ryanodine, Ca^{2+}-chelating agents, or the NCX inhibitor KB-R7943 to prevent diastolic Ca^{2+} overload. After induction of I_{NaL} with ATX-II, in the presence of the abovementioned agents, EADs, but no DADs, were observed in this setting. This leads to the suggestion that DADs occur in settings of Ca^{2+} overload, while formation of EADs is Ca^{2+} independent. The suppression of DADs by ranolazine was further demonstrated in several conditions with enhanced I_{NaL} such as human heart failure [64], pressure-induced heart failure [6], or hypertrophic cardiomyopathy [8].

Based on this promising experimental data, the antiarrhythmic effects of ranolazine were observed in clinical trials. Most information on antiarrhythmic effects of ranolazine were gathered from the MERLIN-TIMI 36 trial. The MERLIN-TIMI 36 trial evaluated ranolazine in patients with non-ST elevation acute coronary syndromes (NSTE-ACS). In contrast to the CAST Study, the incidence of sudden cardiac death was not increased. In fact, there was a numerical reduction of sudden cardiac death close to 45% in patients with a left ventricular

ejection fraction <40% where I_{NaL} is expected to be enhanced. Moreover, treatment with ranolazine significantly reduced the incidence of non-sustained ventricular tachycardia (more than eight beats) by ~35% [65]. Elevated levels of the B-type natriuretic peptide (BNP), as it is known for heart failure, are known to be linked with increased risk in ACS patients. Interestingly, in a subgroup of patients from the MERLIN-TIMI 36 trial, who had elevated BNP levels, the combined primary end points out of cardiovascular death, myocardial infarction, and recurrent ischemia were reduced significantly [66]. As mentioned before, ranolazine causes a slight prolongation of the QTc interval. In a retrospective analysis, NSTE-ACS patients with prolonged QTc interval were observed to have an increased risk for sudden cardiac death. At this point, it should be mentioned that treatment with ranolazine was not associated with increased risk for sudden cardiac death compared to placebo in those patients [67]. In other clinical studies, ranolazine caused a modest QTc interval prolongation, whereas in patients with long QT syndrome type 3, QTc interval was shortened [68, 69]. Experimental data showed ranolazine to inhibit I_{NaL} with a higher potency than other currents like I_{Kr} which would explain shortening of the AP in contrast to prolongation due to I_{Kr} under conditions of an enhanced I_{NaL} [70].

Besides the MERLIN-TIMI 36 study, other studies also report inhibition of I_{NaL} with ranolazine to act antiarrhythmic. Nevertheless, most other studies are case reports or not randomized or placebo controlled. A case series including eight patients suffering from cardiomyopathy reported a 60% reduction of premature ventricular contraction (PVC) burden in six patients with >10% PVCs. In two patients, a PVC-induced cardiomyopathy was supposed, which was normalized after treatment with ranolazine. Additionally, in two patients with sustained ventricular tachycardia, ranolazine terminated the tachycardia and therefore prevented shocks from the implantable cardioverter defibrillator (ICD) [71]. Another study examined patients with ischemic heart disease suffering from antiarrhythmic drug refractory ventricular tachycardia and ICD shocks. Ninety-two percent of the patients had a significant reduction of VTs and no ICD shocks over a follow-up of 6 months under ranolazine medication [72].

Besides the effects of I_{NaL} in the ventricle, I_{NaL} and its inhibition have also been evaluated in the atria. Atrial fibrillation (AF) is the most common arrhythmia associated with increased rate of morbidity and mortality and is often associated with heart failure. In atrial myocytes from AF patients, I_{NaL} was also found to be enhanced, while $I_{Na,peak}$ was decreased [15]. However, the formation of arrhythmias in atria is rather complex than in ventricles, and antiarrhythmic properties of ranolazine in atria also include a relevant inhibition of $I_{Na,peak}$ [15, 73, 74]. Nevertheless, in atrial myocytes isolated from AF patients, CaMKII-dependent SR-Ca^{2+} leak and elevated diastolic Ca^{2+} levels were found [62, 75]. Inhibition of I_{NaL} in atrial myocytes was shown to reduce CaMKII activation and SR-Ca^{2+} leak due to reduced RyR phosphorylation at the CaMKII-specific binding site [62, 75]. Therefore, it is likely that I_{NaL} plays a role in atrial fibrillation and that relevant anti-AF effects of ranolazine are attributed to I_{NaL} inhibition via reduced proarrhythmogenic diastolic SR-Ca^{2+} release.

The MERLIN-TIMI 36 study showed ranolazine to significantly reduce supraventricular tachycardia and paroxysmal atrial fibrillation in patients with ACS although the incidence of AF was very low [65, 76]. Later larger trials were started, investigating the efficiency and safety of ranolazine alone (RAFFAELLO) or in combination with low-dose dronedarone (HARMONY) for the treatment of paroxysmal atrial fibrillation. Treatment with ranolazine was shown to be safe but ranolazine alone did not significantly reduce recurrence of AF significantly, although pooled data from the 500 and 750 mg groups were close to significance ($p = 0.051$) [77]. Nevertheless, as it was a small phase 2 study, this data shows a promising potential of ranolazine in atrial fibrillation which needs to be confirmed in further specifically designed trials. A combination of ranolazine and dronedarone reduced the AF burden up to 70% in patients with paroxysmal AF in the HARMONY trial [78].

Another drug, GS-458967, has been introduced recently as a selective I_{NaL} blocker [79, 80]. In contrast to ranolazine, GS-458967 has more selective effects on I_{NaL}-mediated parameters. Surprisingly, atrial cells were more sensitive to I_{NaL} inhibition by GS-458967 than ventricles. However, in ventricles, GS-458967 causes abbreviation of APD during long QT conditions only, suggesting its pathology-specific effects [81]. Nevertheless, GS-458967 reduced ventricular depolarization and repolarization heterogeneity during acute myocardial ischemia in a porcine model [82]. Administration of GS-458967 provided protection against catecholamine-induced ventricular tachycardia and T wave alternans [83]. GS-458967 did not cause alteration in PR and QT intervals or QRS duration as well as in heart rate and arterial blood pressure [82, 83]. One other group demonstrated suppressive effects of GS-458967 on aconitine-induced ventricular tachycardia and fibrillation in rat hearts [84]. However, by now, there is no clinical data for this drug.

A very recent discovery of a potent I_{NaL} inhibitor is the drug eleclazine (GS-6615). Its selectivity has been improved over ranolazine and showed 42 times more potency than ranolazine with EC_{50} 8000 nM [85]. In contrast to ranolazine, eleclazine reduces potently I_{NaL} but has no major alterations of other ion currents such as I_{CaL},I_{Kr}, I_{Ks}, and peak I_{Na} [86]. Of note, eleclazine is proved to be superior over flecainide also in suppressing ventricular tachycardia and T wave alternans in a catecholamine-induced porcine model [87].

A recent phase 1 trial showed eleclazine to be safe in patients with type 3 long QT syndrome. Phase 2 and 3 trials to treat long QT-3 syndrome, hypertrophic cardiomyopathy

(LIBERTY-HCM), and ventricular arrhythmias in patients with implanted ICDs (TEMPO) were started [88]. Recently, it was reported that the recruitment of the TEMPO trial was stopped because it failed effectivity. Later, LIBERTY-HCM and the trial for long QT-3 syndrome were also stopped [89]. However, to draw distinct conclusions from these trials, the final results have to be published.

Conclusion

An enhanced I_{NaL} has been described to play a crucial role for cellular electrophysiology in several cardiac pathologies such as heart failure. Promising experimental data could show that inhibition of an enhanced I_{NaL} has the potential to suppress arrhythmias in vitro and in vivo.

Ranolazine as a clinically approved drug for the treatment of ischemia has the potential for dual suppression of atrial and ventricular arrhythmias. This has been demonstrated also in some clinical studies. Nevertheless, future work should concentrate on prospective randomized trials, and more specific designed studies are necessary to prove a significant role of I_{NaL} inhibition in clinical antiarrhythmic treatment.

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Compliance with Ethical Standards

Conflict of Interest Philipp Bengel and Shakil Ahmad each declare no potential conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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