CONTEMPORARY REVIEW

Cardiac late Na^+ current: Proarrhythmic effects, roles in long QT syndromes, and pathological relationship to CaMKII and oxidative stress

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Myocyte sodium channel current that persists throughout the plateau of the cardiac action potential is referred to as *late sodium current* ($I_{Na\text{-}L}$). The magnitude of $I_{Na\text{-}L}$ is normally small, but can increase significantly in common acute and chronic pathological settings as a result of inherited and/or acquired Na^+ channelopathies that alter channel opening and closing (ie, gating), location (trafficking), or anchoring and interactions with cytoskeletal proteins. An increase in $I_{Na\text{-}L}$ reduces repolarization reserve in atrial and ventricular myocytes and prolongs the action potential duration and the QT interval. An enhanced $I_{Na\text{-}L}$ is a cause of long QT syndrome 3. $I_{Na\text{-}L}$ may be a cause of afterdepolarizations, triggered arrhythmias, and spontaneous diastolic depolarization–induced automaticity. In addition, enhancement of $I_{Na\text{-}L}$ increases both the temporal and the spatial dispersion of repolarization in the myocardium and may lead to spatially discordant action potential duration alternans, wavebreak, and reentrant arrhythmias. Positive feedback loops between increases in $I_{Na\text{-}L}$ and the activity of Ca^{2+}/calmodulin-dependent protein kinase II appear to contribute to the genesis of arrhythmias and to certain abnormalities of the ischemic heart. In this review, we discuss some of the more relevant experimental results, clinical findings, and insights from cellular and animal models that highlight the role of $I_{Na\text{-}L}$ in the genesis of arrhythmias, long QT syndromes, and intracellular Ca^{2+} homeostasis.

KEYWORDS Repolarization reserve; Dispersion of repolarization; Ranolazine; Long QT syndrome; Antiarrhythmic drug; Afterpotential; Triggered activity; Reentry

ABBREVIATIONS **AP** = action potential; **APD** = action potential duration; **ATX-II** = anemone toxin II; **$[Ca^{2+}]_i$** = intracellular calcium concentration; **CaMKII** = Ca^{2+}/calmodulin-dependent protein kinase II; **DAD** = delayed afterdepolarization; **EAD** = early afterdepolarization; **$I_{Ca\text{-}L}$** = L-type calcium current; **I_{Kr}** = rapidly activating delayed rectifier potassium current; **I_{Ks}** = slowly activating delayed rectifier potassium current; **I_{Na}** = sodium current; **$I_{Na\text{-}L}$** = late sodium current; **I_{NCX}** = sodium/calcium exchange current; **LQT** = long QT; **LQT3** = long QT syndrome 3; **$[Na^+]_i$** = intracellular sodium concentration; **NCX** = Na^+/Ca^{2+} exchange(r); **PI3K** = phosphoinositide 3-kinase; **QTc** = corrected QT; **ROS** = reactive oxygen species; **TTX** = tetrodotoxin; **VT** = ventricular tachycardia

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Introduction

The voltage-gated sodium channel $Na_V1.5$ is highly expressed in cardiac myocytes. Depolarization causes these channels to open briefly, permitting a large entry of Na^+ that peaks in approximately 1 ms and further depolarizes the cell to generate the upstroke of an action potential (AP). After opening, most Na^+ channels quickly inactivate to prevent passage of Na^+ and remain inactivated throughout the duration of the AP plateau. However, Na^+ channel inactivation may be either delayed or reversed to allow channel reopenings (referred to as *late openings*) before repolarization of the AP. Channel late openings allow influx of Na^+ that generates a small "late" current ($I_{Na\text{-}L}$) that persists throughout the AP plateau. It is increasingly recognized that in a variety of pathophysiological settings (inherited and acquired; Table 1), the number of Na^+ channel late openings and thus the amplitude of $I_{Na\text{-}L}$ during the AP plateau is significantly increased. The $I_{Na\text{-}L}$-induced increase in inward current during the AP plateau acts to slow repolarization and prolong the action potential duration (APD). It may also increase the intracellular sodium concentration ($[Na^+]_i$), which, in turn, can lead to an increase in intracellular calcium concentration ($[Ca^{2+}]_i$). Each of these changes is proarrhythmic.[1]

The discovery that long QT (LQT) syndrome could be caused by mutations in cardiac ion channels was the

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Table 1 Pathological conditions, pharmacological agents, toxins, and diseases reported to increase cardiac I_{Na-L}

Conditions/endogenous agents
Activation of CaMKII[1–7]
Activation of Fyn tyrosine kinase[8]
Activation of PKC[9]
Angiotensin II[10,11]
Carbon monoxide[12,13]
2,3-Diphosphoglycerate[14]
Hydrogen peroxide[15–19]
Hypoxia[19–23]
Lysophosphatidylcholine[24–26]
Nitric oxide[27]
Palmitoyl-L-carnitine[28,29]
Stretch[30]
Thrombin[31]
Thyroid hormone T3[32,33]
Drugs and toxins
Aconitine[34,35]
ATX-II, anthopleurin-A[36–41]
Batrachotoxin[42,43]
DPI 201-106[44–46]
BDF9148[47]
KB130015[48,49]
Ouabain (indirectly)[50]
Pyrethroids (tefluthrin)[38,51,52]
Veratridine[53,54]
Diseases
Acquired
Ischemia[22]
Heart failure[55–66]
Hypertrophic cardiomyopathy[67–69]
Diabetic cardiomyopathy[70]
Atrial fibrillation (permanent)[71]
Inherited
LQT3 (*SCN5A*)[72–74]
LQT9 (*CAV3*)[75]
LQT10 (*SCN4B*)[76]
LQT12 (*SNT000A1*)[77,78]
Rett (*Mecp2*) syndrome[79]

References cited in the table are available in the Online Supplement.

ATX-II = anemone toxin II; CaMKII = Ca^{2+}/calmodulin-dependent protein kinase II; I_{Na-L} = late sodium current; LQT# = long QT syndrome #; PKC = protein kinase C.

Modified from Shryock et al.[1]

foundation for a renaissance in the investigation and understanding of mechanisms of arrhythmias. Gain-of-function mutations in the *SCN5A* gene that encodes the pore-forming α subunit of the Na^+ channel $Na_V1.5$ were found in a subset of patients with LQT syndrome (ie, long QT syndrome 3 [LQT3]).[2,3] Many of these mutations disrupt Na^+ channel inactivation and are associated with a phenotype of increased I_{Na-L}, APD prolongation, increased variability in APD, afterdepolarizations, and episodes of polymorphic ventricular tachycardia.

In this review, the proarrhythmic consequences of increasing I_{Na-L} in the heart, and thus the potential antiarrhythmic benefits of inhibiting I_{Na-L}, are identified. Roles of I_{Na-L} in LQT syndromes and the interrelationships between I_{Na-L} and other cellular messengers (ie, Ca^{2+}, reactive oxygen species [ROS], and protein kinases) are emphasized. Additional information and references to the original work on cardiac I_{Na-L} are provided in recent reviews,[1,4–10] which are not cited herein to minimize the length of the reference list.

Arrhythmogenic consequences of an enhanced I_{Na-L}

Three major electrophysiological events provide the mechanistic basis for the initiation and maintenance of cardiac arrhythmias: afterpotentials (early and delayed), automaticity, and reentry. As described below and illustrated in Figure 1, I_{Na-L} causes and/or contributes to all these 3 proarrhythmic events[1,4] by one of the following mechanisms.

Reduced repolarization reserve, AP prolongation, and early afterdepolarizations

During the AP plateau (phase 2 of the AP), I_{Na-L} increases slowly.[5] I_{Na-L} is an inward current that reduces the net repolarizing current (ie, repolarization reserve) and prolongs the AP (Figure 2). Relative to repolarizing currents that flow during the AP plateau or during repolarization, the density of I_{Na-L} is (1) comparable in size but opposite in direction to the slowly activating delayed rectifier potassium current (I_{Ks}), (2) approximately 50% of the rapidly activating delayed rectifier potassium current (I_{Kr}), and (3) approximately 30% of the inward rectifier potassium current (I_{K1}).[5] When I_{Na-L} is increased and/or K^+ currents are inhibited, the APD prolongs, and this can facilitate the formation of early afterdepolarization (EAD).[5,11] EADs may propagate as a wavefront that underlies premature ventricular or atrial complexes.[5,11,12] The inward currents responsible for the upstroke of EAD may include the L-type calcium current (I_{Ca-L}),[11] the forward mode of the sodium/calcium exchange current (I_{NCX}),[5] and sodium current (I_{Na}).[13] On the basis of mathematical models of canine Purkinje and ventricular cell electrophysiology, Li and

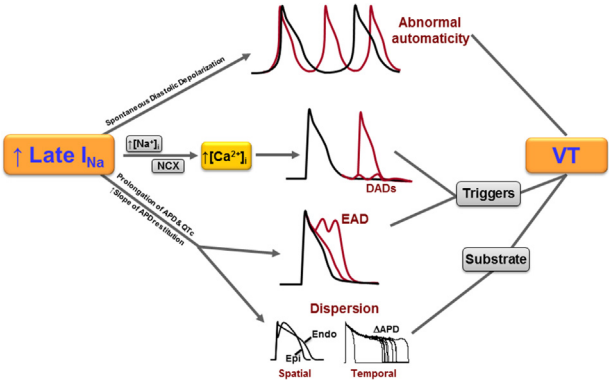

Figure 1 Electrophysiological mechanisms underlying the proarrhythmic effects of I_{Na-L}: spontaneous diastolic depolarization; Na^+ influx coupled to NCX-mediated Ca^{2+} loading and DADs; and prolongation of APD, steepened AP restitution curve, and increased spatial and temporal dispersion of repolarization in the myocardium. AP = action potential; APD = action potential duration; $[Ca^{2+}]_i$ = intracellular calcium concentration; DAD = delayed afterdepolarization; EAD = early afterdepolarization; I_{Na} = sodium current; I_{Na-L} = late sodium current; QTc = corrected QT; $[Na^+]_i$ = intracellular sodium concentration; NCX = Na^+/Ca^{2+} exchanger; VT = ventricular tachycardia. Modified from Figure 1 of Shryock et al.[1]